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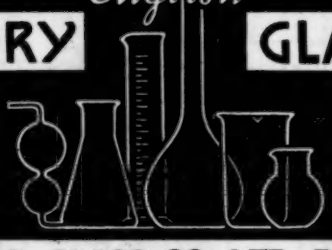

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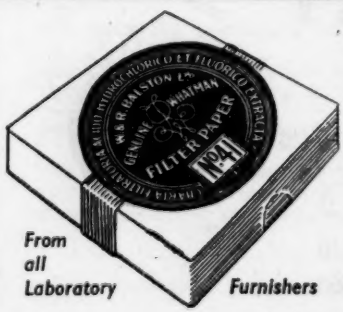

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JOURNAL
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1. *The Conversion of Sucrose into Furan Compounds. Part II. Some 2 : 5-Disubstituted Tetrahydrofurans and their Products of Ring Scission.*

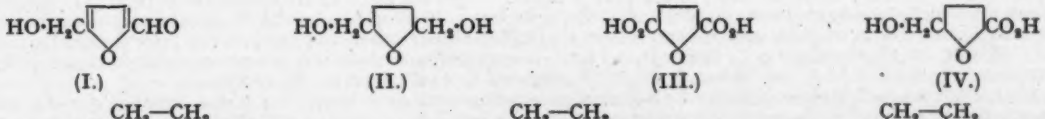
By W. N. Haworth, W. G. M. Jones, and L. F. Wiggins.

5-Hydroxymethylfurfuraldehyde is converted into 2 : 5-*bishydroxymethyltetrahydrofuran* and 5-hydroxymethylfuran-2-carboxylic acid into the corresponding tetrahydrofuran derivative by catalytic hydrogenation. Some derivatives of these compounds are described together with the products obtained by their ring fission. A new synthesis of adipic acid is recorded.

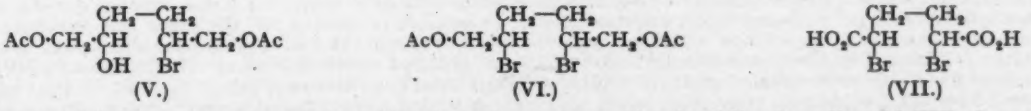
The preparation from sucrose of 5-hydroxymethylfurfuraldehyde has been described (J., 1944, 667) and it is envisaged that this compound might be an intermediate in the conversion of sucrose into useful compounds. We have now investigated the conversion of 5-hydroxymethylfurfuraldehyde into open-chain compounds. This may be accomplished in two ways: (i) by cleavage of the furan ring with hydrolytic agents, and (ii) by cleavage of the reduced furan ring. As examples of the first method may be considered the conversion of furfurylacrylic acid into 4-ketopimelic acid by treatment with ethyl-alcoholic hydrogen chloride (Marckwald, *Ber.*, 1887, **20**, 2811) and the conversion of δ-furfurylidenelævulic acid into 4 : 7-diketosebacic acid (Kehrer and Hofacker, *Annalen*, 1896, **294**, 165). An example of the second method is the cleavage of the tetrahydrofuran ring in 2 : 5-dimethyltetrahydrofuran by hydrogen halides (Freid and Kleene, *J. Amer. Chem. Soc.*, 1941, **63**, 2691) with the formation of 2 : 5-dihalogenohexanes. Ring fission of the tetrahydrofuran ring can also be brought about by acetyl chloride or acetic anhydride. Thus Paul obtained methyl 5-chloro-2-acetoxyvalerate from methyl tetrahydrofuran-2-carboxylate and acetyl chloride (*Compt. rend.*, 1941, **212**, 401) and 1 : 2 : 5-triacetoxypentane from acetoxymethyltetrahydrofuran and acetic anhydride in the presence of zinc chloride (*Bull. Soc. chim.*, 1941, **8**, 369). We have used method (ii) in the work described in this paper in obtaining open-chain compounds from 5-hydroxymethylfurfuraldehyde.

Relatively few 2 : 5-disubstituted derivatives of tetrahydrofuran have so far been described in the literature. Amongst these are 2 : 5-dimethyltetrahydrofuran obtained from the corresponding furan derivative by catalytic hydrogenation over palladised asbestos (Shuikin, Nikiforov, and Stolyarova, *J. Gen. Chem., U.S.S.R.*, 1937, **7**, 1501) and *cis*-tetrahydrofuran-2 : 5-dicarboxylic acid, which can be prepared, amongst other ways, by the action of alcoholic potassium hydroxide on *meso*-2 : 5-dibromoadipic acid. The preparation of this acid by the catalytic hydrogenation of furan-2 : 5-dicarboxylic acid (dehydromucic acid) has apparently not been described. On the other hand, many monosubstituted derivatives of tetrahydrofuran derived from the commercially available furfuraldehyde are known, *e.g.*, tetrahydrofuran-2-carboxylic acid and the corresponding 2-hydroxymethyl and 2-methyl derivatives.

5-Hydroxymethylfurfuraldehyde (I), readily prepared from sucrose (see J., 1944, 667), has been subjected to hydrogenation over Raney nickel and converted into 2 : 5-*bishydroxymethyltetrahydrofuran* (II) in excellent yield. This formed a liquid *bisacetoxy*-derivative and was characterised by the formation of a *bis*- 3 : 5-*dinitrobenzoate*.



(I.) (II.) (III.) (IV.)



(V.) (VI.) (VII.)

Unsuccessful attempts were made to oxidise it to the corresponding 2 : 5-dicarboxylic acid (III), degradation products only being formed. Thus oxidation with chromic anhydride led to complete degradation, and with nitric acid, succinic and oxalic acids were obtained.

Experiments on the ring fission of 2 : 5-bisacetoxymethyltetrahydrofuran were carried out and the following results obtained. On treatment at room temperature with a mixture of acetic anhydride, acetic acid and sulphuric acid, reagents used successfully in the acetolysis of benzylidene derivatives of the hexahydric alcohols (see, for example, Hann, Hudson, and Wolff, *J. Amer. Chem. Soc.*, 1942, **64**, 1493), the compound underwent ring fission to a small extent (10%) and crystalline 1 : 2 : 5 : 6-*tetra-acetoxyhexane* was isolated. Deacetylation

by the Zemplén catalytic method gave crystalline 1 : 2 : 5 : 6-tetrahydroxyhexane (m. p. 98°), probably identical with one of the products (m. p. 95·5°) obtained by Wagner (*Ber.*, 1888, **21**, 3343) by the oxidation of diallyl with potassium permanganate. 2 : 5-Bisacetoxymethyltetrahydrofuran on treatment with hydrogen bromide in glacial acetic acid gave 2 : 5-*dibromo*-1 : 6-*diacetoxyhexane* (VI). 2-Bromo-5-hydroxy-1 : 6-diacetoxyhexane (V) is probably the first product of the reaction and in fact 2-*bromo*-1 : 5 : 6-*triacetoxyhexane* was produced as a by-product.

5-Hydroxymethylfurfuraldehyde can easily be converted into the corresponding carboxylic acid by oxidation with alkaline silver oxide (Reichstein, *Helv. Chim. Acta*, 1926, **9**, 1066). Hydrogenation of the carboxylic acid over Raney nickel led to the formation of a resinous material, probably a polymer of the polyester type, which, however, was readily broken down on treatment with ethyl-alcoholic hydrogen chloride; the product isolated was *ethyl* 5-*hydroxymethyltetrahydrofuran*-2-*carboxylate* and was characterised by the formation of a crystalline *amide*. The compound was better prepared by the hydrogenation of ethyl 5-hydroxymethylfuran-2-carboxylate. The free carboxylic acid was obtained by hydrolysis of the ethyl ester. The hydroxyl group in ethyl 5-hydroxymethyltetrahydrofuran-2-carboxylate was acetylated, and *ethyl* 5-*acetoxymethyltetrahydrofuran*-2-*carboxylate* isolated in good yield. *Ethyl* 5-*chloromethyltetrahydrofuran*-2-*carboxylate* was prepared from the corresponding hydroxy-compound by treatment with thionyl chloride and pyridine. Ring fission of ethyl 5-acetoxymethyltetrahydrofuran-2-carboxylate was effected by the use of the acetolysing reagent (acetic anhydride, acetic acid and sulphuric acid) and took place to a greater extent than in the case of 2 : 5-bis-acetoxymethyltetrahydrofuran. Thus *ethyl* 2 : 5 : 6-*triacetoxyhexoate* was obtained in 55% of the theoretical yield.

5-Hydroxymethyltetrahydrofuran-2-carboxylic acid (IV) was oxidised with nitric acid, and *cis*-tetrahydrofuran-2 : 5-dicarboxylic acid (III) isolated in 60% yield. Attempts to prepare this dibasic acid by the catalytic hydrogenation of furan-2 : 5-dicarboxylic acid led only to poor yields of the desired product and the reduction was only accomplished by the use of high temperatures and pressures with Raney nickel as the catalyst. The catalytic hydrogenation of methyl furan-2 : 5-dicarboxylate was not accomplished.

The investigation of the ring fission of *cis*-tetrahydrofuran-2 : 5-dicarboxylic acid (III) led to a synthesis of adipic acid as below described. The dibasic acid was heated with hydrogen bromide in glacial acetic acid at 125° under pressure, and *meso*-2 : 5-dibromoadipic acid (VII) obtained in 60% yield. Catalytic hydrogenation of the latter over Raney nickel in the presence of calcium carbonate gave adipic acid in good yield. The series of reactions which constitute a synthesis of adipic acid from sucrose is as follows:

Sucrose → 5-Hydroxymethyl-furfuraldehyde → 5-Hydroxymethyl-furan-2-carboxylic acid → 5-Hydroxymethyl-tetrahydrofuran-2-carboxylic acid → *cis*-Tetrahydrofuran-2 : 5-dicarboxylic acid. → *meso*-2 : 5-Dibromo-adipic acid → Adipic acid

Tetrahydrofuran-2 : 5-dicarboxylic acid proved to be a very stable compound. It was recovered unchanged after treatment with nitric acid at 95° and after treatment with fuming hydrochloric acid under pressure. The comparative stability of this ompound is further exemplified by the fact that *methyltetrahydrofuran*-2 : 5-*dicarboxylate*, obtained by boiling the corresponding dicarboxylic acid with methyl-alcoholic hydrogen chloride and characterised as its crystalline *diamide*, did not undergo ring cleavage on treatment with the acetolysing reagent.

Experimental.

2 : 5-*Bishydroxymethyltetrahydrofuran*.—5-Hydroxymethylfurfuraldehyde (10 g.), dissolved in ether (600 c.c.), was hydrogenated over Raney nickel at 130°/75 atms. for 6 hours. After filtration and evaporation of the filtrate the product, 2 : 5-*bishydroxymethyltetrahydrofuran*, distilled at 120° (bath temp.)/0·07 mm. as a fairly mobile, colourless liquid, $n_D^{19°}$ 1·4760. It was soluble in alcohol, acetone and water, slightly soluble in ether, and insoluble in light petroleum (Found: C, 54·7; H, 9·5. $C_6H_{12}O_4$ requires C, 54·6; H, 9·1%). A crystalline 3 : 5-*dinitrobenzoate* was obtained and had m. p. 173° (Found: C, 46·5; H, 3·4; N, 10·9. $C_{20}H_{16}O_{13}N_4$ requires C, 46·2; H, 3·1; N, 10·8%).

2 : 5-*Bisacetoxymethyltetrahydrofuran*.—2 : 5-Bishydroxymethyltetrahydrofuran (6 g.) was refluxed for 15 minutes with acetic anhydride (50 c.c.) and sodium acetate (6 g.), the product poured on ice, the acetic acid neutralised with sodium bicarbonate, and the solution extracted with chloroform. After the extract had been dried over anhydrous magnesium sulphate, it was evaporated to dryness, and a liquid obtained which distilled at 115° (bath temp.)/0·015 mm. The product was a colourless mobile liquid, $n_D^{19°}$ 1·4515. Yield, almost quantitative (Found: C, 55·5; H, 7·7. $C_{10}H_{16}O_6$ requires C, 55·5; H, 7·4%).

Acetolysis of 2 : 5-*Bisacetoxymethyltetrahydrofuran*.—The material (4·2 g.) was dissolved at 0° in the acetolysing reagent, prepared by mixing at 0° acetic anhydride (35 c.c.), acetic acid (15 c.c.), and concentrated sulphuric acid (1 c.c.) (see, for example, Hann, Hudson, and Wolff, *loc. cit.*), and was kept at room temperature for 24 hours. Thereafter it was poured on ice, neutralised with sodium bicarbonate, and extracted with ether. After the extract had been dried over anhydrous magnesium sulphate, it was evaporated to a syrup, which was distilled and collected in two fractions: Fraction 1 (2·6 g.), b. p. 140°/0·03 mm., $n_D^{19°}$ 1·4517; fraction 2 (1·2 g.), b. p. 170°/0·03 mm., $n_D^{19°}$ 1·4480. Both fractions were partly crystalline and after drying on porous tile the crystalline material in each was separately collected and recrystallised from ether–light petroleum. Each sample had m. p. 78°, either separately or in admixture. Yield, 0·21 g. (Found: C, 53·3; H, 6·6. $C_{14}H_{22}O_8$ requires C, 52·9; H, 6·9%). The material was 1 : 2 : 5 : 6-*tetra-acetoxyhexane*. Fraction 1 had *O*-acetyl, 42·4%, and fraction 2 had *O*-acetyl, 45·4%. The presence of only tetra-acetoxyhexane and

bisacetoxymethyltetrahydrofuran being assumed, fraction 1 contains 0·26 g. of the former and fraction 2, 0·4 g. Thus the calculated yield of tetra-acetoxyhexane is 10·3% of the theoretical.

The crystalline tetra-acetoxyhexane was deacetylated by treatment with a trace of sodium in dry methyl-alcoholic solution in the usual way. A crystalline compound resulted, which, on being twice recrystallised from ethyl acetate–alcohol, had m. p. 98° and was 1 : 2 : 5 : 6-tetrahydroxyhexane. It was probably identical with one of the products of the action of potassium permanganate on diallyl (Wagner, *loc. cit.*) (Found : C, 48·5; H, 9·3. Calc. for $C_6H_{14}O_4$: C, 48·0; H, 9·3%).

Treatment of 2 : 5-*Bisacetoxymethyltetrahydrofuran with Hydrogen Bromide in Glacial Acetic Acid.*—The substance (4·4 g.) was dissolved in glacial acetic acid (4 c.c.), and the solution saturated at room temperature with dry hydrogen bromide, heated in a sealed tube at 125° for 2 hours, poured on ice, and extracted with ether. The extract was washed with sodium bicarbonate solution and with water, dried over anhydrous magnesium sulphate, and evaporated. A syrup (5 g.) was obtained which distilled in two fractions : Fraction 1, b. p. 105° (bath temp.)/0·008 mm., a very mobile, colourless liquid (1·2 g.), $n_D^{23°}$ 1·4806, was 2-*bromo*-1 : 5 : 6-*triacetoxyhexane* (Found : C, 42·7; H, 5·65; Ac, 36·8. $C_{12}H_{19}O_8Br$ requires C, 42·8; H, 5·6; Ac, 38·1%). Fraction 2, b. p. 145° (bath temp.)/0·08 mm., a fairly viscid, yellow liquid (3·8 g.), $n_D^{22°}$ 1·4957, was mainly 2 : 5-*dibromo*-1 : 6-*diacetoxyhexane* (Found : C, 33·2; H, 4·5; Ac, 26·8. $C_{10}H_{16}O_4Br_2$ requires C, 33·3; H, 4·4; Ac, 24·0%).

Oxidation of 2 : 5-*Bishydroxymethyltetrahydrofuran.*—A solution of the material (0·5 g.) in nitric acid (*d* 1·15) (30 c.c.) was slowly warmed to 100° and kept thereat for 1 hour, vigorous evolution of nitrous fumes occurring. The solution was diluted with water and evaporated at constant volume until most of the excess of nitric acid had disappeared. On evaporation to dryness a solid residue was left which after recrystallisation from ether gave (*a*) oxalic acid dihydrate (m. p. 101°) and (*b*) succinic acid (m. p. 186°).

Ethyl 5-*Hydroxymethyltetrahydrofuran*-2-*carboxylate.*—(*a*) 5-Hydroxymethylfuran-2-carboxylic acid (5 g.) was dissolved in water (500 c.c.) and hydrogenated over Raney nickel at 165°/60 atms. for 10 hours. On evaporation a red-brown resinous material remained, which was refluxed with ethyl alcohol (150 c.c.) containing 2% of hydrogen chloride for 7 hours. After neutralisation with silver carbonate, filtration and evaporation, a mobile liquid was obtained which distilled at 85° (bath temp.)/0·02 mm. and showed $n_D^{17°}$ 1·4540. Yield, 3·58 g. The distillate was a colourless mobile liquid, soluble in alcohol, ether, acetone and chloroform and slightly soluble in light petroleum.

(*b*) Ethyl 5-hydroxymethylfuran-2-carboxylate (35 g.) in ethyl acetate (600 c.c.) was hydrogenated over Raney nickel (1 g.) at 140°/130 atm. for 7 hours. Filtration of the resulting solution and evaporation of the solvent gave a mobile liquid, b. p. 85° (bath temp.)/0·02 mm., identical in properties with the material obtained in (*a*) ; this was *ethyl* 5-*hydroxymethyltetrahydrofuran*-2-*carboxylate*. Yield, 29 g. (Found : OEt, 25·3. $C_8H_{14}O_4$ requires OEt, 25·9%).

Ethyl 5-*Chloromethyltetrahydrofuran*-2-*carboxylate.*—Ethyl 5-hydroxymethyltetrahydrofuran-2-carboxylate (2 g.) was dissolved in dry pyridine (0·93 c.c.), and thionyl chloride (1·14 c.c.) carefully added at 0°. The mixture was heated at 100° for 1 hour, ether added, and the mixture washed successively with water, sodium bicarbonate solution, and water. After being dried over anhydrous magnesium sulphate, the ether was removed; the resulting liquid distilled at 82° (bath temp.)/0·023 mm. The product had $n_D^{25°}$ 1·4585 and was a colourless mobile oil. Yield, 0·75 g. The *chloromethyl* derivative was insoluble in water, very slightly soluble in light petroleum, and soluble in alcohol, ether, acetone, and chloroform (Found : C, 50·3; H, 6·5; OEt, 22·0. $C_8H_{13}O_3Cl$ requires C, 49·9; H, 6·7; OEt, 23·2%).

Ethyl 5-*Acetoxymethyltetrahydrofuran*-2-*carboxylate.*—The 5-hydroxymethyl ester (3 g.) was refluxed for 1 hour with acetic anhydride (10 c.c.) and fused sodium acetate (1·5 g.), and the solution poured into water and neutralised with sodium bicarbonate. The mixture was then extracted with ether, and the extract dried over anhydrous magnesium sulphate. Distillation of the solvent gave a liquid which distilled as a colourless mobile oil at 115° (bath temp.)/0·03 mm., $n_D^{21°}$ 1·4453. Yield, 80% of the theoretical (Found : Ac, 23·0. $C_{10}H_{16}O$ requires Ac, 20·0%).

5-*Hydroxymethyltetrahydrofuran*-2-*carboxyamide.*—A solution of the ethyl ester (0·2 g.) in ethyl alcohol (3 c.c.) was saturated with ammonia at 0°, kept at 0° for 24 hours, the solvent and ammonia then evaporated, and the residue recrystallised from acetone; m. p. 99°. Yield, 0·12 g. (Found : C, 49·7; H, 7·6; N, 10·3. $C_6H_{11}O_3N$ requires C, 49·7; H, 7·6; N, 9·7%).

5-*Hydroxymethyltetrahydrofuran*-2-*carboxylic Acid.*—The ethyl ester (6 g.) was heated at 70° with a slight excess of hydrated barium hydroxide (6·3 g.) for 1 hour, N-sulphuric acid added exactly to precipitate the barium as sulphate, which was removed by centrifuging, the supernatant liquid evaporated, and the residue extracted with chloroform. Evaporation of this extract gave a moderately viscid liquid which did not crystallise (Found : equiv., 150. $C_6H_{10}O_4$ requires equiv., 146).

Acetolysis of Ethyl 5-*Hydroxymethyltetrahydrofuran*-2-*carboxylate.*—The ester (0·5 g.) was added to a mixture of acetic anhydride (9 c.c.), acetic acid (4 c.c.), and concentrated sulphuric acid (0·25 c.c.) at 0°, the whole kept at room temperature for 40 hours and poured on ice, and the resulting solution extracted with chloroform. The extract was washed free from acid with dilute sodium bicarbonate solution, dried over anhydrous magnesium sulphate, and evaporated to dryness. The resulting syrup was distilled in two fractions : (*a*) Ethyl 5-acetoxymethyltetrahydrofuran-2-carboxylate (0·12 g.), b. p. 115° (bath temp.)/0·03 mm., $n_D^{21°}$ 1·4453 (Found : Ac, 21·8; OEt, 19·7. Calc. for $C_{10}H_{16}O_5$: Ac, 20·0; OEt, 20·8%). (*b*) *Ethyl* 2 : 5 : 6-*triacetoxyhexoate* (0·4 g.), b. p. 150° (bath temp.)/0·05 mm., $n_D^{21°}$ 1·4434 (Found : Ac, 36·7; OEt, 13·5. $C_{14}H_{22}O_8$ requires Ac, 38·1; OEt, 14·1%).

Oxidation of 5-*Hydroxymethyltetrahydrofuran*-2-*carboxylic Acid with Nitric Acid.*—The acid (5·5 g.) was dissolved in nitric acid (70 c.c., *d* 1·42) and heated at 80° until oxidation was complete. The solution, after dilution with water, was evaporated several times until the nitric acid had gone. The product was a crystalline solid, m. p. 126—127° after recrystallisation from ether–petrol and was *cis*-tetrahydrofuran-2 : 5-dicarboxylic acid (yield, 60% of the theoretical); the m. p. was not depressed by an authentic specimen prepared from *meso*-2 : 5-dibromoadipic acid by the method of Le Sueur and Haas (J., 1910, **97**, 173). The mother-liquors on evaporation gave a crystalline residue of indefinite m. p., probably a mixture of the *cis*- and the *trans*-isomer of the dicarboxylic acid.

Furan-2 : 5-*dicarboxylic Acid.*—Potassium hydrogen saccharate was boiled with 60% hydrobromic acid for 36 hours, and the required acid, m. p. 342°, isolated by Phelps and Hale's method (*J. Amer. Chem. Soc.*, 1901, **23**, 445). Yield, 56% of the theoretical. The substance was obtained in colourless plates after being treated with animal charcoal, but even the purest specimens reduced Fehling's solution.

Methyl Furan-2 : 5-*dicarboxylate.*—The dicarboxylic acid (20 g.) was boiled with 2% methyl-alcoholic hydrogen chloride for 6 hours. The main bulk of the ester crystallised on cooling and the remainder was obtained by neutralising the filtrate with silver carbonate, evaporating the solution, and recrystallising the residue from methyl alcohol. Yield, 90% of the theoretical, m. p. 110°.

Hydrogenation of Furan-2 : 5-*dicarboxylic Acid.*—The acid (10 g.), dissolved in 600 c.c. of water, was heated at 235° for 8 hours with Raney nickel (0·7 g.) at 135 atms. of hydrogen. On evaporation the solution gave a thick resinous mass, which appeared to be a polymer. The product was boiled for 5 hours with 2% methyl-alcoholic hydrogen chloride (100 c.c.), the acid neutralised with silver carbonate, and the solution filtered and evaporated. The residue was a mobile liquid (2·6 g.), b. p. 110—130°/0·04 mm., $n_D^{20°}$ 1·4505, which contained methyl tetrahydrofuran-2 : 5-dicarboxylate. A

sample of the distillate (1 g.) was hydrolysed by heating with a solution of hydrated barium hydroxide (1·8 g.) for 2 hours at 80°. After exact neutralisation with N-sulphuric acid, removal of barium sulphate, and evaporation of the filtrate to dryness, the residue obtained was extracted with acetone, and the extract evaporated to give a crystalline residue, from which *cis*-tetrahydrofuran-2 : 5-dicarboxylic acid, m. p. 126°, was obtained in small yield.

Methyl cis-*Tetrahydrofuran*-2 : 5-*dicarboxylate*.—The dicarboxylic acid (1 g.) was dissolved in 1% methyl-alcoholic hydrogen chloride and boiled for 5 hours. The acid was neutralised with silver carbonate, the solution filtered, and the filtrate evaporated to give a liquid (1·1 g.), b. p. 90° (bath temp.)/0·03 mm., $n_D^{15°}$ 1·4550 (Found: OMe, 32·4. $C_8H_{12}O_5$ requires OMe, 33·0%).

cis-*Tetrahydrofuran*-2 : 5-*dicarboxyamide*.—A solution of the methyl ester (0·3 g.) in dry methyl alcohol (10 c.c.) was saturated with ammonia at 0° and kept overnight at this temperature, the solvent and ammonia then removed in a vacuum, and the residue recrystallised from acetone–methyl alcohol. Yield, 0·21 g., m. p. 189° (Found: C, 45·9; H, 6·0; N, 17·8. $C_6H_{10}O_3N_2$ requires C, 45·6; H, 6·3; N, 17·7%).

Attempted Acetolysis of Methyl Tetrahydrofuran-2 : 5-*dicarboxylate*.—The ester (0·8 g.) was dissolved in 20 c.c. of the acetolysing reagent (acetic anhydride 15 c.c., acetic acid 4·6 c.c., concentrated sulphuric acid 0·4 c.c.) at 0°, kept at room temperature for 10 days, and poured into ice-water; after being neutralised with sodium bicarbonate, the solution was extracted with chloroform. The extract on evaporation gave a liquid (0·6 g.), b. p. 90—100° (bath temp.)/0·03 mm., $n_D^{15°}$ 1·4555 (Found: OMe, 32·5. Calc. for $C_8H_{12}O_5$: OMe, 33·0%), which was unchanged starting material.

Ring Fission of cis-*Tetrahydrofuran*-2 : 5-*dicarboxylic Acid with Hydrogen Bromide in Glacial Acetic Acid*.—The dicarboxylic acid (0·65 g.) was dissolved in glacial acetic acid (7 c.c.). A solution, saturated at 0°, of hydrogen bromide in glacial acetic acid (3·5 c.c.) was added, and the mixture heated in a sealed tube at 125° for 12 hours. The solution was poured into ice-water and extracted with ether, the extract dried (anhydrous magnesium sulphate), filtered, and evaporated, and the residue recrystallised from formic acid. The product was *meso*-2 : 5-dibromoadipic acid identical with the product obtained by Le Sueur and Haas (*loc. cit.*) by the bromination of adipyl chloride. Yield, 0·7 g., 60% of the theoretical, m. p. 192—194°.

Conversion of meso-2 : 5-*Dibromoadipic Acid into Adipic Acid*.—The dibromo-acid (2 g.) (m. p. 191°) was reduced with hydrogen over Raney nickel at 90 atms. for 4 hours at 125° in water in the presence of excess of calcium carbonate. The solution was filtered, evaporated to small bulk, acidified with dilute sulphuric acid, and extracted with ether. The extract, after being dried over magnesium sulphate, was distilled; the residue, on recrystallisation from nitric acid (*d*, 1·47), formed long needles (1 g.), m. p. 151—152°, not depressed by authentic adipic acid.

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A. E. Hills Laboratories, The University, Edgbaston, Birmingham. [*Received, September 12th*, 1944.]

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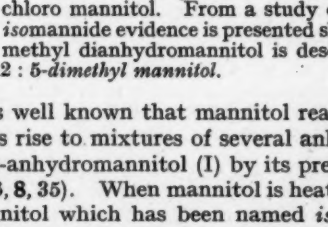
2. *The Anhydrides of Polyhydric Alcohols. Part I. The Constitution of* iso*Mannide.*

By L. F. Wiggins.

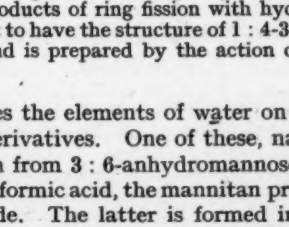
Methods of preparation of *iso*mannide are given, including its production by the dry distillation of 1 : 6-dichloro mannitol. From a study of the products of ring fission with hydrochloric acid and other reactions of *iso*mannide evidence is presented showing it to have the structure of 1 : 4-3 : 6-dianhydromannitol. The 2 : 5-dimethyl dianhydromannitol is described and is prepared by the action of sodium methoxide on 1 : 6-*dichloro* 2 : 5-*dimethyl mannitol*.

It is well known that mannitol readily loses the elements of water on being heated alone or with acids and gives rise to mixtures of several anhydro-derivatives. One of these, named mannitan, has been shown to be 3 : 6-anhydromannitol (I) by its preparation from 3 : 6-anhydromannose (Valentin, *Coll. Czech. Chem. Comm.*, 1936, **8**, 35). When mannitol is heated with formic acid, the mannitan produced is accompanied by a dianhydromannitol which has been named *iso*mannide. The latter is formed in a greater proportion if hydrochloric acid is used instead of formic acid (Fauconnier, *Bull. Soc. chim.*, 1884, **41**, 119; *Compt. rend.*, 1885, **100**, 914). These anhydrides are also formed to a smaller extent when mannitol is subjected to dry distillation (Fauconnier, *Compt. rend.*, 1882, **95**, 991).

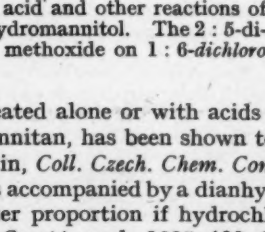
More convenient methods of preparation of *iso*mannide have now been developed. It is formed in 35% yield (i) by heating mannitol, suspended in dichloro glycerol, in a stream of hydrogen chloride, or (ii) by boiling mannitol with fuming hydrochloric acid for 3 days. *iso*Mannide also results from the action of heat on 1 : 6-dichloro mannitol (II), which is itself obtained by the action of fuming hydrochloric acid on mannitol (Haworth, Heath, and Wiggins, J., 1944, 155). 1 : 6-Dichloro mannitol, the structure of which has been established by Micheel (*Annalen*, 1932, **496**, 77) and by Haworth and Wiggins (J., 1944, 58), melts with decomposition at 174°, one product being *iso*mannide. When dichloro mannitol is heated under diminished pressure, hydrogen chloride is evolved and *iso*mannide distils in almost quantitative yield.



(I.)



(II.)



(III.)

The constitution of *iso*mannide has not hitherto been established, although Romburgh and Burg (*Proc. Acad. Sci. Amsterdam*, 1922, **25**, 335) on indirect evidence suggested that it was 1 : 4-3 : 6-dianhydromannitol.

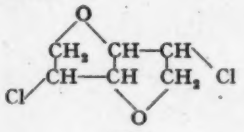
That in fact this is the correct structure is shown in this paper, and *iso*mannide is represented as a dihydroxy-hexahydrodifuran (III).

The description of *iso*mannide as 1 : 4-3 : 6-dianhydromannitol is based on the following experimental evidence.

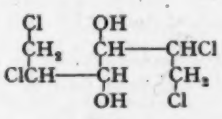
(1) When heated with fuming hydrochloric acid under pressure, *iso*mannide undergoes anhydro ring scission and 1 : 6-dichloro mannitol is obtained. Positions 1 and 6 are therefore involved in the anhydro rings.

(2) Lead tetra-acetate is without action on *iso*mannide, an indication that the two hydroxyl groups are not on adjacent carbon atoms.

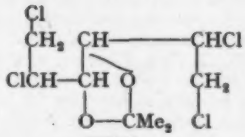
(3) Treatment of *iso*mannide with thionyl chloride and pyridine yields a dichloro dianhydrohexitol (m. p. 67°) which is described as 2 : 5-dichloro dianhydromannitol because its treatment with fuming hydrochloric acid under pressure leads to the production of crystalline 1 : 2 : 5 : 6-*tetrachloro mannitol*, which can be reconverted into the original dichloro mannitol by treatment with sodium methoxide. This tetrachloro-compound was shown to possess the configuration of mannitol inasmuch as it was easily convertible into hexachloro mannitol. Moreover, the given allocation of the chlorine atoms was established by the following synthetic procedure.



(IV.)



(V.)



(VI.)

1 : 6-Dichloro mannitol readily forms a monoacetone compound in which the acetone residue was assigned, without proof, to C_3 and C_4 by Micheel (*Annalen*, 1932, **486**, 77). The author has recently confirmed this view (Wiggins, unpublished work). Treatment of 1 : 6-dichloro 3 : 4-monoacetone mannitol with thionyl chloride and pyridine yielded a non-crystalline *tetrachloro monoacetone* derivative in which the chlorine atoms must be located at C_1, C_2, C_5, and C_6. Acetonisation of the tetrachloro mannitol obtained by the ring opening of dichloro *iso*mannide gave a liquid which was identical with the above in respect of refractive index, boiling point and specific rotation. The product of ring fission of dichloro *iso*mannide with hydrochloric acid must therefore be 1 : 2 : 5 : 6-tetrachloro mannitol (V) and the acetone compound must be represented by (VI).

(4) That the hydroxyl groups of *iso*mannide are located at C_2 and C_5 is further shown by the synthesis of dimethyl *iso*mannide from 1 : 6-*dichloro* 3 : 4-*monoacetone* 2 : 5-*dimethyl mannitol*. The latter compound was prepared by the cautious methylation of the known 1 : 6-dichloro 3 : 4-monoacetone mannitol (Micheel, *loc. cit.*). Its hydrolysis led to the isolation of 1 : 6-*dichloro* 2 : 5-*dimethyl mannitol*, which was converted, by treatment with two equivalents of sodium methoxide, into 2 : 5-*dimethyl* iso*mannide*, identical with the product of direct methylation of *iso*mannide.

(5) It is clear, therefore, that the two anhydro rings of *iso*mannide involve positions 1, 3, 4, and 6 and the substance is to be described as either (*a*) 1 : 4-3 : 6-dianhydro-, or (*b*) 1 : 3-4 : 6-dianhydro-mannitol. That the rings are in fact hydrofuranol [*i.e.*, (*a*)] in type is shown by the following facts: (i) The observation of Fauconnier (*loc. cit.*) that *iso*mannide results from the action of formic acid on 3 : 6-anhydromannitol (mannitan) and that mannitan is now found to give *iso*mannide on distillation in the presence of a drop of sulphuric acid, whereas by itself it distils unchanged. (ii) Mannitan is converted into *iso*mannide by the following series of reactions involving only neutral or alkaline reagents. From mannitan (3 : 6-anhydromannitol) is obtained a liquid *tosyl triacetyl* derivative in which the tosyl group is substituting a primary alcoholic group, proved by the fact that sodium toluene-*p*-sulphonate is obtained in 80% yield when it is treated with sodium iodide in acetone solution. This tosyl triacetyl mannitan on treatment with sodium methoxide gives *iso*mannide identical with the substance obtained by the action of hydrochloric acid on mannitol. This view of the constitution of *iso*mannide is supported by the extreme stability of the ring system in the original dianhydro-compound, the dimethyl and dichloro derivatives. Thus *iso*mannide is not affected by heating under pressure with either methyl-alcoholic sodium methoxide or ammonia; furthermore the ring system is stable to oxidising agents such as nitric acid at 100°, since the dimethyl derivative can be recovered unchanged after several hours' treatment with this reagent. This stability is characteristic of the hydrofuranol structure (cf. Peat and Wiggins, J., 1938, 1088) and in no wise agrees with the expected properties of the four-membered ring system postulated under (*b*) above. This anhydro ring type is found in 1 : 2-monoacetone 3 : 5-anhydroxylose, which easily undergoes ring scission with alkaline reagents (Levene and Raymond, *J. Biol. Chem.*, 1933, **102**, 331).

Experimental.

Treatment of Mannitol with Hydrogen Chloride in Dichloro Glycerol.—Mannitol (20 g.) was suspended in dichloro glycerol (70 c.c.), heated at 140—150°, through which hydrogen chloride was passed. After 1½ hours solution was complete and after 3½ hours' heating the solution was evaporated to a syrup, which distilled at 130—140°/0·03 mm., giving a mobile liquid (6·5 g.), $n_D^{16°}$ 1·5010, which crystallised rapidly on cooling. After being recrystallised from ethyl acetate–alcohol it (5·4 g.) had m. p. 87—88° and $[\alpha]_D$ +91·0° in water (*c*, 2·28) and was dianhydromannitol identical with the *iso*mannide of Fauconnier (*loc. cit.*).

Treatment of Mannitol with Concentrated Hydrochloric Acid.—Mannitol (500 g.) was dissolved in fuming hydrochloric acid (3 l.), and the mixture boiled for 72 hours; the acid solution was then evaporated to a syrup, and the last traces of

hydrochloric acid removed by evaporation with water. Finally the syrup was distilled on the water-pump at 180—200°. The distillate (140 g.) crystallised completely and was recrystallised from ethyl acetate containing a little alcohol (m. p. 87°). Other volatile products were obtained which are being investigated.

Action of Heat on 1 : 6-*Dichloro Mannitol.*—1 : 6-Dichloro mannitol (2 g.) was heated in a vacuum at 180°. Evolution of hydrogen chloride occurred and the mass became more mobile and eventually distilled completely. The distillate (1·2 g.) crystallised on cooling; recrystallised from ethyl acetate, it formed prismatic crystals (0·95 g.), m. p. 87°, not depressed by authentic 1 : 4-3 : 6-dianhydromannitol.

2 : 5-*Dichloro* 1 : 4-3 : 6-*Dianhydromannitol.*—Dianhydromannitol (4 g.) was dissolved in dry pyridine (5·6 g.), and thionyl chloride (6·4 g.) carefully added at 0°. The mixture was warmed on the water-bath to 90°, sulphur dioxide then being evolved. After being heated for ½ hour at 100°, the mixture was poured into water, the filtered solution extracted with chloroform, and the extract washed with sodium bicarbonate solution and with water and dried over anhydrous magnesium sulphate. On evaporation a crystalline residue (4 g.) was obtained which, recrystallised from ether–petrol, formed long needles (3·3 g.; 70% of the theoretical), m. p. 67°, $[\alpha]_D$ +93·5° in chloroform (*c*, 2·054) (Found: C, 39·4; H, 4·2; Cl, 38·5. $C_6H_8O_2Cl_2$ requires C, 39·2; H, 4·4; Cl, 39·0%). The *substance* was extremely stable, being recovered unchanged by distillation with fused caustic potash.

2 : 5-*Dimethyl* 1 : 4-3 : 6-*Dianhydromannitol.*—Dianhydromannitol (1 g.) was treated four times with methyl iodide and silver oxide at 45°, the product being extracted after each treatment with boiling chloroform. The crystalline *substance* finally obtained, recrystallised from ether–petrol, formed thin leaflets (0·9 g.), m. p. 75—76°, $[\alpha]_D^{18°}$ +175·0° in chloroform (*c*, 2·287) (Found: C, 54·6; H, 8·4; OMe, 34·8. $C_8H_{14}O_4$ requires C, 55·0; H, 8·1; OMe, 35·4%).

Treatment of Dianhydromannitol with Hydrochloric Acid.—Dianhydromannitol (1 g.), dissolved in fuming hydrochloric acid (20 c.c.), was heated for 24 hours in a sealed tube. On evaporation a semi-crystalline mass was obtained; from its solution in a little alcohol–water, crystals of 1 : 6-dichloro mannitol (0·25 g.) separated, m. p. 174° (Bouchardat, *Bull. Soc. chim.*, 1873, **19**, 199, gives m. p. 174°).

Lack of Action of Alkaline Reagents on the Dianhydromannitol.—(a) *Methyl-alcoholic ammonia.* Dianhydromannitol (1 g.) was heated at 120° for 20 hours with methyl alcohol (50 c.c.) saturated with ammonia at 0°. The solution, on evaporation, gave a syrup which crystallised on nucleation with dianhydromannitol. Recrystallisation from ethyl acetate–alcohol gave unchanged dianhydromannitol (0·8 g.), m. p. 87°.

(b) *Sodium methoxide.* Dianhydromannitol (1 g.) was heated at 120° for 20 hours with excess of 10% methyl-alcoholic sodium methoxide. The solution was diluted with water and evaporated to dryness after neutralisation with 5N-sulphuric acid. Extraction of the residue with ethyl acetate gave unchanged dianhydromannitol (0·75 g.), m. p. 87°.

Non-oxidation of 2 : 5-*Dimethyl Dianhydromannitol with Nitric Acid.*—The substance (0·5 g.), dissolved in nitric acid (*d* 1·4; 10 c.c.), was heated at 100° for 4 hours without the occurrence of any obvious reaction. Water was added, and the nitric acid removed by evaporation at constant volume. After evaporation to dryness the residual syrup was extracted with chloroform, and the extract filtered and evaporated to a crystalline residue, which, recrystallised from ethyl acetate–light petroleum, had m. p. 75°, not depressed by the original material. Yield, 0·35 g. (Found: OMe, 36·0. Calc. for $C_8H_{14}O_4$: OMe, 35·4%). The product was therefore unchanged 2 : 5-dimethyl dianhydromannitol.

Treatment of Dianhydromannitol with Lead Tetra-acetate.—Dianhydromannitol (2 g.), dissolved in glacial acetic acid (100 c.c.), was shaken with lead tetra-acetate (6·5 g.; 1·1 mols.) for 48 hours, and the solution poured on ice, neutralised with sodium bicarbonate, filtered, and evaporated to dryness. The residue was extracted with ethyl acetate under reflux and on evaporation of the extract a crystalline residue (1·9 g.) was obtained which, recrystallised from ethyl acetate–alcohol, had m. p. 86—87°, not depressed by the original material. Yield, 1·7 g.

1 : 2 : 5 : 6-*Tetrachloro Mannitol.*—2 : 5-Dichloro dianhydromannitol (7·2 g.), suspended in fuming hydrochloric acid (200 c.c.), was heated in a sealed tube for 72 hours at 110°. After evaporation there remained a syrupy residue A (6 g.). The aqueous distillate contained crystals which had distilled with the water vapour and which, after separation and recrystallisation from light petroleum (yield, 1·6 g.), had m. p. 66°, not depressed by authentic 2 : 5-dichloro dianhydromannitol. The syrupy residue A was dissolved in ether, and a little light petroleum added; the crystals that slowly separated were collected in several fractions, but each melted at 69—70°. Total yield, 3·4 g., $[\alpha]_D$ +28·3° in chloroform (*c*, 3·107) (Found: C, 27·7; H, 4·1; Cl, 54·9. $C_6H_{10}O_3Cl_4$ requires C, 28·1; H, 3·9; Cl, 55·5%). The product was 1 : 2 : 5 : 6-*tetrachloro mannitol.*

There was a residual syrup which did not crystallise but distilled at 135°/0·03 mm. (1·6 g.) (Found: Cl, 50·6%).

1 : 2 : 5 : 6-*Tetrachloro* 3 : 4-*Dibenzoyl Mannitol.*—Tetrachloro mannitol (0·14 g.) was dissolved in dry pyridine (2 c.c.), a slight excess of benzoyl chloride (0·2 c.c.) added, and the mixture kept overnight. The solution was poured into water and extracted with chloroform. The extract was washed successively with 5% sulphuric acid, sodium bicarbonate solution, and water, dried over anhydrous magnesium sulphate, and evaporated to dryness. The syrupy residue crystallised on cooling and, recrystallised from ether–light petroleum, formed stout needles (0·15 g.), m. p. 109—110°, $[\alpha]_D^{15°}$ −95·4° in chloroform (*c*, 1·048) (Found: C, 51·9; H, 3·9; Cl, 31·5. $C_{20}H_{18}O_4Cl_4$ requires C, 51·7; H, 3·8; Cl, 30·6%).

Conversion of 1 : 2 : 5 : 6-*Tetrachloro Mannitol into Hexachloro Mannitol.*—1 : 2 : 5 : 6-Tetachloro mannitol (0·4 g.) was heated with phosphorus pentachloride (1 g.) at 130° for 1 hour, hydrogen chloride being evolved. The mixture was diluted with chloroform and poured on ice, and the chloroform layer separated, washed with sodium bicarbonate solution and with water, dried over anhydrous magnesium sulphate, and evaporated. Recrystallisation from light petroleum gave hexachloro mannitol, m. p. 138°, not depressed by an authentic specimen.

Action of Sodium Methoxide on 1 : 2 : 5 : 6-*Tetrachloro Mannitol.*—Tetrachloro mannitol (1 g.) was dissolved in chloroform (10 c.c.), methyl-alcoholic sodium methoxide (containing 0·45 g. of sodium methoxide) added, and the mixture kept for 4 hours at room temperature. After dilution with water the solution was extracted with chloroform, and the extract washed with water, dried over anhydrous magnesium sulphate, and evaporated to dryness. The residue, recrystallised from light petroleum (yield, 0·5 g.), had $[\alpha]_D$ +91·5° in chloroform (*c*, 1·66), m. p. 67—68°, not depressed by authentic 2 : 5-dichloro dianhydromannitol.

Acetonisation of 1 : 2 : 5 : 6-*Tetrachloro Mannitol.*—Tetrachloro mannitol (0·3 g.) was shaken overnight with dry acetone (25 c.c.) containing concentrated sulphuric acid (0·1 c.c.). The acid was neutralised with anhydrous sodium carbonate, and the solution filtered and evaporated to a syrup, which distilled at 115° (bath temp.)/0·05 mm. and was 1 : 2 : 5 : 6-*tetrachloro* 3 : 4-*monoacetone mannitol.* Yield 0·33 g., $n_D^{15°}$ 1·4954, $[\alpha]_D^{20°}$ +56·8° in chloroform (*c*, 2·405) (Found: C, 36·5; H, 4·7. $C_9H_{14}O_3Cl_4$ requires C, 36·5; H, 4·7%).

Chlorination of 1 : 6-*Dichloro* 3 : 4-*Monoacetone Mannitol.*—The material (Micheel, *Annalen*, 1932, **497**, 77) (1 g.) was dissolved in dry pyridine (5 g.), thionyl chloride (4 g.) added at 0°, and the mixture warmed to 100°, evolution of sulphur dioxide then occurring. After being kept thereat for 1 hour, the mixture was poured on ice, the filtered solution extracted with chloroform, and the extract washed successively with sodium bicarbonate solution and water. On evaporation a syrup was obtained, which was purified by extraction with ether, filtration, evaporation, and distillation of the product. The material distilled at 115° (bath temp.)/0·05 mm. and was 1 : 2 : 5 : 6-tetrachloro 3 : 4-monoacetone mannitol (0·4 g.), $n_D^{18°}$ 1·4955, $[\alpha]_D^{18°}$ +57·3° in chloroform (*c*, 1·99) (Found: C, 37·0; H, 4·6; Cl, 47·4. Calc. for $C_9H_{14}O_3Cl_4$: C, 36·5; H, 4·7; Cl, 48·0%).

1 : 6-*Dichloro* 3 : 4-*Monoacetone* 2 : 5-*Dimethyl Mannitol*.—Dry 1 : 6-dichloro 3 : 4-monoacetone mannitol (5 g.) was treated with excess of dry methyl iodide and dry silver oxide at 45° for 9 hours, and after evaporation of the methyl iodide the residue was extracted several times with boiling chloroform. After five such treatments the product distilled at 110° (bath temp.)/0·02 mm. Yield, 3·83 g. The distillate partly crystallised; it was drained on tile, and the product recrystallised from ether–petrol. 1 : 6-*Dichloro* 3 : 4-*monoacetone* 2 : 5-*dimethyl mannitol* had m. p. 56°, $[\alpha]_D$ +11·5° in chloroform (*c*, 2·253). Yield, 1·6 g. (Found: C, 45·8; H, 6·7; Cl, 25·0; OMe, 20·6. $C_{11}H_{20}O_4Cl_2$ requires C, 46·0; H, 7·0; Cl, 24·7; OMe, 21·6%).

1 : 6-*Dichloro* 2 : 5-*Dimethyl Mannitol*.—The preceding compound (0·503 g.) was dissolved in 75% alcohol containing 5% sulphuric acid (40 c.c.) and kept at room temperature, and the reaction followed polarimetrically: $[\alpha]_D$ +9·5° (initial value); +3·0° (48 hrs.); +1·6° (74 hrs.); −3·2° (95 hrs.); −16·0° (168 hrs.); −25·4° (312 hrs.); −30·2° (383 hrs.); −35·0° (550 hrs.). The solution was thereafter neutralised with barium carbonate, filtered, and evaporated to dryness. The residue was extracted with chloroform, and the extract evaporated to small bulk. The crystals that separated were recrystallised from chloroform, giving 1 : 6-*dichloro* 2 : 5-*dimethyl mannitol* (0·21 g.), m. p. 131° (Found: C, 38·5; H, 6·1; OMe, 24·4. $C_8H_{16}O_4Cl_2$ requires C, 38·9; H, 6·4; Cl, 28·7; OMe, 24·8%).

Action of Sodium Methoxide on 1 : 6-*Dichloro* 2 : 5-*Dimethyl Mannitol*.—1 : 6-Dichloro 2 : 5-dimethyl mannitol (0·17 g.) was dissolved in chloroform (5 c.c.), methyl alcohol (2 c.c.) containing sodium (0·04 g.) added, and the mixture kept at room temperature overnight; sodium chloride had then separated. The mixture was diluted with water and extracted with chloroform, the extract dried over anhydrous magnesium sulphate and evaporated to dryness, and the crystalline residue recrystallised from ether–light petroleum, giving 2 : 5-dimethyl dianhydromannitol (0·09 g.), m. p. and mixed m. p. 75—76° (Found: OMe, 35·6. Calc. for $C_8H_{14}O_4$: OMe, 35·2%).

Mannitan.—Mannitol (500 g.) was boiled with concentrated hydrochloric acid (2 l.) for 12 hours only. The resulting solution was evaporated, and the syrup obtained dissolved in alcohol and allowed to crystallise. After 3 days the crystals which had separated were collected and recrystallised several times from alcohol–water; m. p. 145—147°, identical with that given by Valentin (*loc. cit.*). Yield, 25·5 g. The filtrates were evaporated, and the residue used to prepare *iso*mannide.

Dry Distillation of Mannitan.—Mannitan (2 g.) was distilled under reduced pressure (10 mm.) over a gauze, practically without decomposition; yield of distillate which crystallised completely, 1·8 g. Recrystallised from alcohol–water, it had m. p. 145—147° and was identical with the original material.

Dry Distillation of Mannitan in the Presence of Acid Catalysts.—Mannitan (2 g.) was melted, 2 drops of concentrated sulphuric acid added, and the mixture distilled over a gauze at 10 mm. Water distilled first, followed by *iso*mannide (1·1 g.), which, recrystallised from ethyl acetate, had m. p. and mixed m. p. 86—87°.

Conversion of Mannitan into iso*Mannide with Alkaline Reagents*.—Mannitan (5 g.) was dissolved in dry pyridine (50 c.c.), and tosyl chloride (6 g.) carefully added at 0°. The mixture was kept at room temperature for 96 hours, acetic anhydride (25 c.c.) being added after the first 48 hours. The solution was poured on ice and extracted with chloroform. The extract was washed successively with 5% sulphuric acid, sodium bicarbonate solution, and water, dried over anhydrous magnesium sulphate, and evaporated. Yield, 10·5 g. The product, however, was a liquid which has, so far, defied attempts at crystallisation. It was 1-*tosyl* 2 : 4 : 5-*triacetyl mannitan* (Found: S, 7·3. $C_{19}H_{24}O_{10}S$ requires S, 7·3%).

Detosylation. The material (10 g.) was dissolved in chloroform (50 c.c.), and methyl alcohol (30 c.c.) containing sodium (2·1 g.) added at 0°. The solution was kept overnight, diluted with chloroform, and extracted with water. The aqueous extracts were combined, neutralised with N-sulphuric acid, and evaporated to dryness in the presence of barium carbonate. The dry residue was extracted with boiling ethyl acetate, the extract evaporated, and the product distilled at 140—160°/0·08 mm. Yield, 1·6 g.; 50% of the theoretical. The distillate crystallised; recrystallised from ethyl acetate, it formed prisms, m. p. 86—87° alone or in admixture with authentic *iso*mannide.

Treatment of 1-*Tosyl* 2 : 4 : 5-*Triacetyl Mannitan with Sodium Iodide in Acetone*.—The liquid monotosyl triacetyl mannitan (5·6 g.) was dissolved in dry acetone (50 c.c.) containing dry sodium iodide (4 g.), and the solution heated at 100° for 12 hours under pressure. The liquid was filtered, and the precipitate of sodium toluene-*p*-sulphonate washed with acetone and dried in a vacuum. Yield, 1·9 g.; 78% of the theoretical.

The author thanks Professor W. N. Haworth, F.R.S., and Dr. S. Peat for their interest, Mr. A. E. James for his assistance, and I.C.I. (Dyestuffs Division) for a grant in support of this work.

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3. *The Condensation of Fluorene with Acetone. Part III. Formation of Fluoranthene Derivatives.*

By Harold France, S. Horwood Tucker, and (in part) James Forrest.

Methyl β-9-fluorenyl-β-methyl-*n*-propyl ketone (I) has been cyclised to 2 : 2 : 4-trimethyl-1 : 2-dihydrofluoranthene (III) * by the action of hydrogen bromide.

The ketone (I) has been converted into 2 : 2 : 4-trimethyl-1 : 2 : 3 : 4-tetrahydrofluoranthene (IV) either by cyclisation by means of hydrogen iodide or by conversion with aluminium *iso*propoxide into the intermediate alcohol, δ-9-*fluorenyl*-δ-*methylpentan*-β-*ol* (V), followed by elimination from the latter compound of the elements of water.

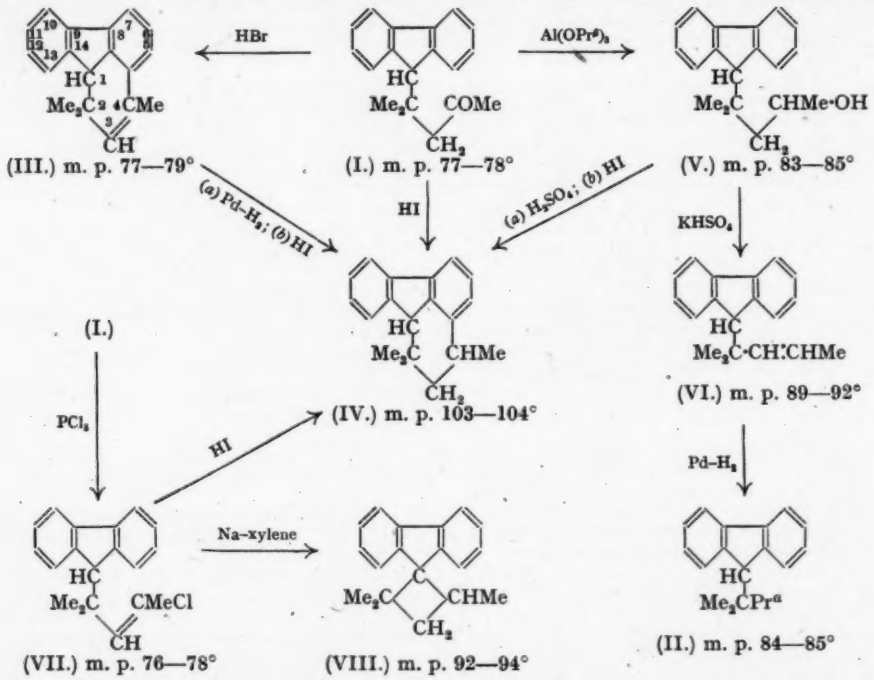
The ketone (I) has been treated with phosphorus pentachloride to form β-*chloro*-δ-9-*fluorenyl*-δ-*methyl*-Δβ-*pentene* (VII), which, by reaction with sodium in boiling xylene, has given *fluorene*-9-spiro-2′ : 2′ : 4′-*trimethyl*-cyclo*butane* (VIII).

Oxidation of the compounds (III) and (IV) to 1-*acetylfluorenone* and thence to fluorenone-1-carboxylic acid furnishes proof that they are derivatives of fluoranthene.

It has been shown [Maitland and Tucker, J., 1929, 2559 (Part I); France, Maitland, and Tucker, J., 1937, 1739 (Part II)] that fluorene and acetone in presence of potassium hydroxide combine to give methyl β-9-fluorenyl-β-methyl-*n*-propyl ketone (I). Reduction of (I) gave rise to several products, depending on the reducing agent used; *e.g.*, reduction by either the Kishner–Wolff or the Clemmensen method gave

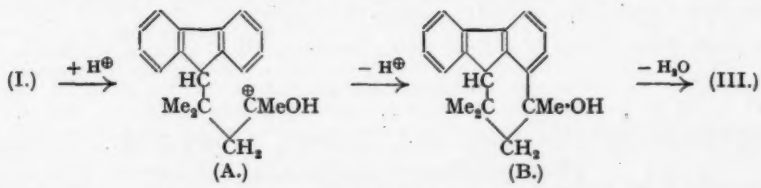
* The numbering follows von Braun and Anton (*Ber.*, 1934, **67**, 1051; cf. *idem*, *ibid.*, 1929, **62**, 147).

β-9-fluorenyl-β-methylpentane (II); but in the latter reaction a substance, $C_{19}H_{20}$, m. p. 103—104°, was also obtained. This substance was also prepared by the action of hydriodic acid in boiling acetic acid on the ketone



(I). Furthermore, by the action of hydrobromic acid in acetic acid, the ketone (I) gave a substance, $C_{19}H_{18}$, m. p. 77—79°, which by catalytic hydrogenation gave the above substance, $C_{19}H_{20}$.

We have now established that oxidation of these substances, of formulæ $C_{19}H_{18}$ and $C_{19}H_{20}$ respectively, by sodium dichromate in boiling glacial acetic acid gives an intermediate compound, 1-*acetylfluorenone*, and finally fluorenone-1-carboxylic acid (maximum yield, 53%). It is therefore evident that the two hydrocarbons are derivatives of fluoranthene, *viz.*, 2 : 2 : 4-trimethyl-1 : 2-dihydrofluoranthene (III) ($C_{19}H_{18}$) and 2 : 2 : 4-trimethyl-1 : 2 : 3 : 4-tetrahydrofluoranthene (IV) ($C_{19}H_{20}$), being produced by ring-closure involving the 1-position in the fluorene nucleus. Presumably (see Berliner, *J. Amer. Chem. Soc.*, 1942, **64**, 2894; Bradsher and Smith, *ibid.*, 1943, **65**, 854) the reaction of the ketone (I) with hydrogen bromide may be formulated thus:



The solution of hydrobromic acid converts the ketone (I), by addition of a proton to the carbonyl group, into the hypothetical intermediate compound (A), which by virtue of its carbonium atom and an electrophilic attack on the carbon atom in position 1 in the fluorene nucleus effects ring closure, a proton being liberated. Facile dehydration of the tertiary alcohol (B) produces 2 : 2 : 4-trimethyl-1 : 2-dihydrofluoranthene (III).

Attempts to cyclise the ketone (I) to give (III) by means of acetic anhydride containing a few drops of concentrated sulphuric acid failed (cf. Bradsher, *J. Amer. Chem. Soc.*, 1943, **65**, 451).

When the ketone (I) was boiled with hydriodic acid (*d* 1·7) in acetic acid, as previously reported (France, Maitland, and Tucker, *loc. cit.*), the substance $C_{19}H_{20}$, m. p. 103—104°, was obtained: it is undoubtedly 2 : 2 : 4-trimethyl-1 : 2 : 3 : 4-tetrahydrofluoranthene (IV). It has not yet been established whether its formation is to be interpreted as (*a*) analogous to that suggested for the action of hydrobromic acid on (I), followed by reduction of (III) to (IV), or (*b*) as reduction of (I) to δ-9-fluorenyl-δ-methylpentan-β-ol (V), which then, instead of undergoing normal reduction to the hydrocarbon (II), eliminates water and cyclises to the fluoranthene derivative (IV) in the usual manner.

That the second mechanism is probable is substantiated by the following: Reduction of the ketone (I) by aluminium *iso*propoxide in *iso*propyl alcohol gave δ-9-*fluorenyl*-δ-*methylpentan*-β-*ol* (V), which (*a*) by boiling with hydriodic acid (*d* 1·5) in acetic acid for 20 minutes, or (*b*) by the action of concentrated sulphuric acid in glacial acetic acid at room temperature, at once gave (IV). Furthermore, attempts to reduce (III) to (IV) by

boiling with hydriodic acid (*d* 1·7) in acetic acid for 4 hours—the conditions under which (I) gives (IV) (France, Maitland, and Tucker, *loc. cit.*, p. 1742; and this communication)—gave only a very small yield of (IV).

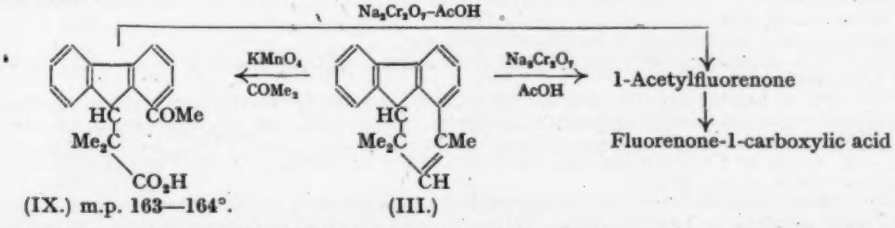
Heating the alcohol (V) with potassium hydrogen sulphate gave an olefin which is probably *δ-9-fluorenyl-δ-methyl-*Δ^{β}*-pentene* (VI) (or possibly δ-9-fluorenyl-δ-methyl-Δ^{α}-pentene). Catalytic hydrogenation (palladium–acetic acid) of the olefin (VI) gave the expected pentane (II).

The original ketone (I) reacted with phosphorus pentachloride in chloroform to give probably *β-chloro-δ-9-fluorenyl-δ-methyl-*Δ^{β}*-pentene* (VII) (or the corresponding Δ^{α}-derivative), which, by the action of hydriodic acid (*d* 1·7) in boiling acetic acid, gave the fluoranthene derivative (IV); oxidation of (VII) with sodium dichromate in glacial acetic acid gave fluorenone, thus proving that the chlorine atom is in the open chain and not in the fluorene nucleus.

The chloro-compound (VII), on boiling with sodium in xylene, gave *fluorene*-9-spiro-2′ : 2′ : 4′-*trimethylcyclobutane* (VIII). Oxidation of this compound gave an unidentifiable oil: neither fluorenone nor any acidic product could be obtained. The oil did not react with hydroxylamine.

Oxidation of 2 : 2 : 4-trimethyl-1 : 2-dihydrofluoranthene (III) by sodium dichromate solution in boiling glacial acetic acid for 1½ hours gave rise to 1-*acetylfluorenone*, m. p. 114—116° (yield, 10%), and fluorenone-1-carboxylic acid (yield, 31%), which softened at 188° and melted at 191—194° (Ray and Rieveschl, *J. Amer. Chem. Soc.*, 1943, **65**, 836, give m. p. 193—194°; Fieser and Seligman, *ibid.*, 1935, **57**, 2174, m. p. 191—193°; Huntress, Pfister, and Pfister, *ibid.*, 1942, **64**, 2845, m. p. 188—190°). When the oxidation mixture was boiled for 24 hours, fluorenone-1-carboxylic acid only was obtained (crude, 64%; pure, 53%) [cf. 52% obtained by the oxidation of fluoranthene (Ray and Rieveschl, *loc. cit.*)]. 1-Acetylfluorenone gives a dioxime, but the substance obtained by the action of 2 : 4-dinitrophenylhydrazine on 1-acetylfluorenone gave inexplicable analytical results; the constitution of 1-acetylfluorenone was, however, established by the above oxidation, and by oxidation by means of sodium hypochlorite solution to fluorenone-1-carboxylic acid. Oxidation of 2 : 2 : 4-trimethyl-1 : 2 : 3 : 4-tetrahydrofluoranthene (IV) by dichromate as above (25 hours) gave 1-acetylfluorenone (4%) and fluorenone-1-carboxylic acid (28%).

It is now clear that the substance $C_{19}H_{18}O_3$, m. p. 163—164°, obtained by permanganate–acetone oxidation of 2 : 2 : 4-trimethyl-1 : 2-dihydrofluoranthene (III) (France, Maitland, and Tucker, *loc. cit.*, p. 1743) is 1-*acetylfluorene*-9-iso*butyric acid* (IX); and since it has now been shown that this acid is oxidised by dichromate–acetic acid to 1-acetylfluorenone and fluorenone-1-carboxylic acid, the course of oxidation is probably as shown:



(IX.) m.p. 163—164°. (III.)

(III) and (IV) have no growth-inhibitory effect (Badger, Elson, Haddow, Hewett, and Robinson, *Proc. Roy. Soc.*, 1942, *B*, **130**, pp. 268, 270) and no carcinogenic activity (Badger, Cook, Hewett, Kennaway, Kennaway, and Martin, *ibid.*, 1942, *B*, **131**, 170).

Experimental.

2 : 2 : 4-*Trimethyl*-1 : 2-*dihydrofluoranthene* (III).—The method formerly adopted for the preparation of (III) (France, Maitland, and Tucker, *loc. cit.*, p. 1743) has been improved: Hydrogen bromide (prepared by the action of bromine on boiling tetralin) was passed into a solution of the ketone (I) (10 g.) in glacial acetic acid (100 ml.) for 1 hour. Crystals separated; these were removed an hour later and washed with cold glacial acetic acid. The acid washings were added to the filtrate and after 3—4 hours a second crop of crystals was removed. Addition of water to the filtrate, whether otherwise untreated or previously boiled to remove hydrogen bromide, gave only a small amount of oil. The crystalline deposits were dissolved in glacial acetic acid, the solution boiled to expel hydrogen bromide, and, after cooling, the deposited material was crystallised from methanol, giving 2 : 2 : 4-trimethyl-1 : 2-dihydrofluoranthene (III), m. p. 77—79° (5·9 g.; yield, 63%).

Passage of hydrogen bromide until the acetic acid solution of (I) was merely saturated (15 mins.), followed by standing or boiling, gave lowered yields of (III).

2 : 2 : 4-*Trimethyl*-1 : 2 : 3 : 4-*tetrahydrofluoranthene* (IV).—(a) Catalytic hydrogenation of (III) by means of palladium-black–hydrogen–acetic acid gave the hydrocarbon $C_{19}H_{20}$, m. p. 103—104°, now known to be (IV) (yield, 95%) (France, Maitland, and Tucker, *loc. cit.*, p. 1743).

(b) *Action of hydriodic acid on* (I) (France, Maitland, and Tucker, *loc. cit.*, p. 1742). Improved method: The ketone (I) (25 g.) in glacial acetic acid (300 ml.) and hydriodic acid (*d* 1·7, 60 ml.) were boiled together for 5 hours, and the product isolated as before (12 g.; yield, 50%). (IV) was similarly obtained from (III) (very small yield), from the alcohol (V)—boiling for 20 minutes (yield, 50%)—and from the chloro-compound (VII).

(c) *Action of sulphuric acid on the alcohol* (V). The alcohol (V) was dissolved in glacial acetic acid, and an equal volume of a mixture of concentrated sulphuric acid and glacial acetic acid (1 : 1 by vol.) added. The mixture became warm, turned faintly brown, and in a few seconds deposited crystals of (IV) (excellent yield).

An attempt to prepare (IV) by ring closure of the olefin (VI) by using anhydrous aluminium chloride in cold carbon disulphide gave an uncrystallisable oil.

(IV) does not form a picrate (acetic acid solution).

δ-9-*Fluorenyl-δ-methylpentan-β-ol* (V).—The ketone (I) (5·28 g.) was boiled with a molar solution of aluminium *iso*propoxide in *iso*propyl alcohol 25 ml.) with slow distillation of the alcohol, the volume of the reaction mixture being kept

at 25 ml. by periodical additions of *iso*propyl alcohol, until the distillate became free from acetone (2 : 4-dinitrophenylhydrazone test) (5 hours). The reaction mixture became gelatinous. The pale yellow solid precipitated by dilute sulphuric acid crystallised from light petroleum (b. p. 60—80°) in colourless rosettes, m. p. 83—85° (4·4 g.; yield, 85%), of *δ-9-fluorenyl-δ-methylpentan-β-ol* (V) (Found : C, 85·7; H, 8·3. $C_{19}H_{22}O$ requires C, 85·7; H, 8·3%).

The *phenylurethane* of (V), obtained by standing and heating its benzene solution with phenyl *iso*cyanate, gave thick-set rosettes from glacial acetic acid, m. p. 157—159° (Found : C, 81·3; H, 7·0; N, 3·6. $C_{26}H_{27}O_2N$ requires C, 81·0; H, 7·0; N, 3·6%).

The 3 : 5-*dinitrobenzoate* prepared by boiling a solution of (V) with 3 : 5-dinitrobenzoyl chloride in pyridine for 1 minute crystallised from glacial acetic acid in pale green prisms, m. p. 164—165° after softening at 161° (Found : C, 67·7; H, 5·2; N, 6·0. $C_{26}H_{24}O_6N_2$ requires C, 67·8; H, 5·2; N, 6·1%).

The alcohol (V) (1 g.) was heated with potassium hydrogen sulphate (1 g.) for 10 minutes at 180°. The product, isolated in the usual way, was crystallised from acetic acid diluted with a trace of water, then from methanol, and gave *δ-9-fluorenyl-δ-methyl-Δ$^{\beta}$-pentene* (VI) in colourless needles, m. p. 92° after softening at 89° (0·28 g.; yield, 33%) (Found : C, 91·8; H, 8·0. $C_{19}H_{20}$ requires C, 91·9; H, 8·1%). Microhydrogenation, with palladium-black in acetic acid, gave a value corresponding to 1·2 double bonds. The reduction product alone, or mixed with (II) obtained by the Clemmensen method of reduction of the original ketone (I), melted at 84—85°, thus proving that (VI) has an open chain and on hydrogenation gives (II).

β-Chloro-δ-9-fluorenyl-δ-methyl-Δ$^{\beta}$-pentene (VII).—The ketone (I) (5 g.) was heated with phosphorus pentachloride (20 g.) in chloroform (50 ml.) for 1 hour. After the chloroform had been removed by steam-distillation, the residue crystallised from glacial acetic acid in colourless plates, m. p. 76—78° (1·9 g., yield, 30%) (Found : C, 80·7; H, 7·0; Cl, 12·9. $C_{19}H_{19}Cl$ requires C, 80·7; H, 6·7; Cl, 12·6%).

When phosphorus pentabromide was used instead of the chloride in the above process, the dibromo-derivative $C_{19}H_{18}OBr_2$ previously isolated (France, Maitland, and Tucker, *loc. cit.*, p. 1744) was obtained.

Fluorene-9-spiro-2′ : 2′ : 4′-*trimethylcyclobutane* (VIII).—The chloro-compound (VII) (2·82 g.) was boiled in xylene (5 ml.) with finely divided sodium (0·5 g.) for 1 hour; the xylene solution, separated from the purple precipitate, was evaporated; the residue so obtained crystallised from methanol in long colourless prisms (0·94 g.). Treatment of the purple precipitate with ethanol and then with excess of water, followed by extraction with and crystallisation from methanol, gave more of this product (0·15 g.) (total, 1·09; yield, 44%), *fluorene*-9-spiro-2′ : 2′ : 4′-*trimethylcyclobutane*, m. p. 92—94° (Found : C, 91·8; H, 8·1; *M*, 198. $C_{19}H_{20}$ requires C, 91·9; H, 8·1%; *M*, 248).

Oxidation of Fluoranthene Derivatives to 1-Acetylfluorenone and to Fluorenone-1-carboxylic Acid.—Oxidation of 2 : 2 : 4-trimethyl-1 : 2-dihydrofluoranthene (III). The compound (III) (2·46 g.), sodium dichromate (13 g.), and glacial acetic acid (90 ml.) were boiled together for 1½ hours; then more dichromate (10 g.) was added, and boiling continued for 1½ hours. Half the bulk of acetic acid was removed by distillation, and the residual liquor poured into a large excess of dilute sulphuric acid. The washed precipitate was extracted with potassium hydroxide solution; the residue crystallised from methanol to give 1-*acetylfluorenone* in golden sword-blades, m. p. 114—116° (crude, 0·51 g.; pure 0·25 g.; yield, 10%) (Found : C, 80·9; H, 4·4. $C_{15}H_{10}O_2$ requires C, 81·1; H, 4·5%). The alkaline extract on acidification with dilute sulphuric acid gave the characteristic salmon-coloured precipitate of fluorenone-1-carboxylic acid (0·99 g.; yield, 45%). Purification was difficult; repeated crystallisation from glacial acetic acid gave eventually orange-red needles, m. p. 191—193° after softening at 189° (0·7 g.; yield, 31%). A sample of the acid prepared from fluoranthene by oxidation with chromic acid in aqueous acetic acid melted similarly.

2 : 2 : 4-Trimethyl-1 : 2-dihydrofluoranthene (III) under the latter conditions of oxidation gave no acid but appeared to be completely destroyed.

Increasing the period of heating and the amount of dichromate used in the above-described experiment caused increase in the yield of fluorenone-1-carboxylic acid (18 hours; yield, 46%) at the expense of 1-acetylfluorenone: thus when (III) (1·23 g.) was boiled with sodium dichromate (14 g.) in acetic acid (50 ml.) for 24 hours, and the liquor treated as above, only a trace of 1-acetylfluorenone was obtained but an increased yield of fluorenone-1-carboxylic acid (crude, 0·72 g.; pure, 0·60 g.; yield, 53%).

1-Acetylfluorenone gave a *dioxime* which, crystallised from dilute acetic acid and then from toluene, formed pale green nodules, m. p. 197° after softening at 180° (Found : C, 71·2; H, 4·8. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8%).

A *derivative* of 1-acetylfluorenone prepared by the action of 2 : 4-dinitrophenylhydrazine in methanol containing a drop of sulphuric acid crystallised from dioxan, then from toluene, in hairy, orange-yellow crystals, m. p. 251° (decomp.) after softening at 248°, and is of doubtful composition (Found : C, 61·4, 61·5; H, 3·6, 3·6; N, 12·8. A monohydrazone, $C_{21}H_{14}O_5N_4$, would require C, 62·7; H, 3·5; N, 13·9%).

1-Acetylfluorenone (0·12 g.) in warm methanol (5 ml.) was treated with aqueous sodium hypochlorite (5 ml.) and sodium hydroxide solution (10%, 1 ml.) and left for a short time. After filtration, sulphurous acid and dilute sulphuric acid were added to the filtrate. The orange-red precipitate, crystallised from acetic acid, consisted of fluorenone-1-carboxylic acid (0·07 g.; yield, 55%).

1-Acetylfluorenone, dissolved in dioxan containing a drop of benzyltrimethylammonium hydroxide solution, when treated with acrylonitrile and warmed, gave brown crystals from acetic anhydride, m. p. >280°. It was not further characterised (cf. Bruson *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 2457).

Oxidation of 2 : 2 : 4-*Trimethyl*-1 : 2 : 3 : 4-*tetrahydrofluoranthene* (IV).—The substance (1·24 g.) was boiled in glacial acetic acid (50 ml.) containing sodium dichromate (12 g.) for 25 hours. The above method of isolation gave 1-acetylfluorenone (4%) and fluorenone-1-carboxylic acid (28%).

Oxidation of 1-*Acetylfluorene*-9-*isobutyric acid* (IX).—Oxidation with dichromate–acetic acid for 5 hours gave 1-acetylfluorenone (5%) and fluorenone-1-carboxylic acid (22%).

The ketone (I), heated with an ethanol–dilute sulphuric acid solution of 2 : 4-dinitrophenylhydrazine, gave the 2 : 4-*dinitrophenylhydrazone*, which crystallised from glacial acetic acid in orange prisms, m. p. 200—202° (Found : C, 67·7; H, 5·4; N, 12·5. $C_{25}H_{24}O_4N_4$ requires C, 67·6; H, 5·4; N, 12·6%).

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UNIVERSITY OF GLASGOW. [*Received, September 1st*, 1944.]

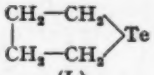
4. *Syntheses of* 1 : 4-*Telluroxan and Related Cyclic Tellurides.*

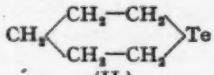
By W. V. Farrar and J. Masson Gulland.

A simple synthesis of *cyclo*tellurobutane (I) and *cyclo*telluropentane (II) derivatives is described, and applied to the preparation of 1 : 4-*telluroxan* (III) and its derivatives. An account is also given of the reaction of tellurium and of sodium telluride with methylene, ethylene, and trimethylene dihalides.

Various cyclic tellurium compounds have been prepared in order to examine the possibility of their use as bactericidal or bacteriostatic agents (see Gulland and Farrar, *Nature*, 1944, **154**, 88), and these will be described in this and subsequent communications.

*cyclo*Tellurobutane (I) and *cyclo*telluropentane (II) (Morgan and Burgess, J., 1928, 321; Morgan and Burstall, J., 1931, 180) were synthesised by two methods: (1) the action of aluminium telluride (Al_2Te_3) on tetramethylene and pentamethylene dihalides between 125° and 175° gave mixtures of the cyclic telluridihalide with complex telluronium salts formed by secondary reactions; although the latter decomposed into the cyclic telluride when distilled in a vacuum, the syntheses are indirect and laborious and the yields were not good. (2) The reaction between tellurium and tetramethylene di-iodide at about 140° gave a good yield of *cyclo*telluributane di-iodide (Morgan and Burstall, *loc. cit.*), but this reaction was alleged by Morgan and Burgess (*loc. cit.*) to be almost a complete failure with pentamethylene dihalides. The present research has shown this to be incorrect; in fact, pentamethylene di-iodide and tellurium react to give the di-iodide of (II) in good yield.


(I.)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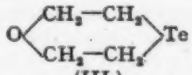
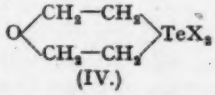

(III.)

A simpler and more satisfactory synthesis of these heterocyclic rings has, however, now been achieved by using sodium telluride, made *in situ* by the reaction of tellurium with a hot aqueous solution of sodium formaldehydesulphoxylate in an inert atmosphere (Tschugaev and Chlopin, *Ber.*, 1914, **47**, 1269). If the resulting solution is refluxed with an alkyl halide, the dialkyl telluride is formed (Balfe, Chaplin, and Phillips, J., 1938, 341; Challenger and Bird, J., 1939, 163; Balfe and Nandi, J., 1941, 70). As was expected, replacement of the alkyl halide by a 1 : 4- or 1 : 5-alkylene dihalide results in ring formation, and no difficulty was experienced in preparing pure *cyclo*telluributane dihalides from tetramethylene dibromide in yields of about 60% (based on tellurium used). Similarly, by using pentamethylene dichloride, *cyclo*telluripentane dihalides were produced, though in rather inferior yield (35%). This low yield is unlikely to be due to a greater reluctance to close a 6-membered than a 5-membered ring; it is probably to be traced to the fact that the slower reaction with the chloride encourages the formation of complex by-products, which was in fact observed. The melting points, solubilities, and general properties of these compounds agree very closely with those reported by Morgan and his co-workers (*locc. cit.*).

Since ββ′-dichlorodiethyl ether is now readily available, this method of ring-synthesis has been applied to the preparation of the hitherto unrecorded 1 : 4-*telluroxan* (III), and a series of its derivatives. 1 : 4-Telluroxan itself, prepared by reducing its dichloride with aqueous potassium metabisulphite, is a foul-smelling, yellow, low-melting solid, which is slowly oxidised in air but when pure is capable of being stored in a sealed tube without undergoing change. With halogens, telluroxan readily forms the stable crystalline *dihalides* (IV, X = halogen) and with methyl iodide gives the water-soluble *methiodide* (V).

When telluroxan dichloride is ground with excess of moist silver oxide, silver chloride is formed, together with a strongly alkaline solution of the *dihydroxide* (IV, X = OH), which can be obtained as a deliquescent, crystalline mass when the aqueous solution is evaporated to dryness under reduced pressure. It is a strong base; halogen acids regenerate the dihalides, and other acids yield a series of well-crystallised hydroxy-salts (VI, X = acid radical), of which the *hydroxy-nitrate*, *-picrate*, and *-picrolonate* were prepared. No indication was observed of the formation of hydroxy-halides.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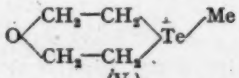
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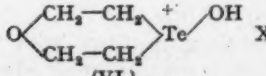
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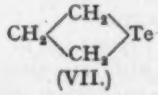
(VII.)

It was noted throughout the work on derivatives of 1 : 4-telluroxan that these are in general more polar in character than the corresponding *cyclo*telluri-pentane or -butane compounds. The dihalides, for example, are not soluble in non-polar solvents, but only in such solvents as alcohol (sparingly) and acetone; *cyclo*telluripentane dihalides, on the other hand, can be recrystallised from light petroleum, and the *cyclo*telluributane dihalides from benzene. The melting points of the telluroxan dihalides are much higher, and their order is Cl > Br > I, the reverse being the case for the other ring-systems. Further, no analogues of the crystalline hydroxy-salts have been recorded for the other cyclic tellurides.

The cause of these interesting differences between compounds of such very similar structure is obscure, but they are paralleled by the contrast between 1 : 4-selenoxan (Gibson and Johnson, J., 1931, 266) and *cyclo*selenopentane (Morgan and Burstall, J., 1929, 2197).

An attempt to make telluroxan di-iodide by the action of tellurium on ββ′-di-iododiethyl ether (Gibson and Johnson, J., 1930, 2526), following Morgan's second general method, was not very successful, probably owing to the instability of the ether, which breaks up on heating, giving iodine. The main product was a dark gum, from which the impure di-iodide could be isolated in 10—13% yield. The pure substance was most easily made by the neutralisation of aqueous telluroxan dihydroxide with hydriodic acid. In contrast to the two well-defined forms of the di-iodides of *cyclo*tellurobutane, *cyclo*telluropentane and *cyclo*telluropentanedione, telluroxan di-iodide appears to exist in only one form.

The study of the ring closure of αω-alkylene dihalides was completed by an investigation of trimethylene and ethylene derivatives.

Trimethylene dibromide reacted readily with aqueous sodium telluride even at room temperature, giving a nauseating substance which could be extracted with chloroform. The extract continually deposited a yellow gummy solid and combined with bromine, forming an ochre-coloured amorphous precipitate insoluble in all the usual solvents. Probably *cyclo*telluropropane (VII) is first formed, but, like the selenium analogue (Morgan and Burstall, J., 1930, 1497), readily polymerises to substances of high molecular weight; *cyclo*selenopropane is, however, sufficiently stable to be isolated. The polymeric dibromide reacted with moist silver oxide to give an alkaline solution, from which halogen acids precipitated gelatinous materials, and picric acid gave an amorphous picrate, soluble in glacial acetic acid, and melting at about 165° (decomp.).

Trimethylene di-iodide and tellurium at 120—150° yielded a black, apparently crystalline mass of very high m. p., almost entirely insoluble in all solvents; it contained some unchanged tellurium.

The reaction between ethylene dibromide and sodium telluride prepared by the Tschugaev–Chlopin method took a rather unexpected course. Neither cyclisation (to 1 : 4-ditelluran) nor polymer formation occurred, but even at room temperature tellurium was precipitated quantitatively and ethylene was liberated: $C_2H_4Br_2 + Na_2Te \longrightarrow C_2H_4 + 2NaBr + Te$.

When tellurium was heated in a sealed tube with ethylene dibromide at 160—170° for 16·5 hours, all but a minute amount was recovered unchanged.

Ethylene iodobromide (Simpson, *Proc. Roy. Soc.*, 1874, 51) was expected to react with tellurium according to the equation $2C_2H_4BrI + Te \longrightarrow (CH_2Br{\cdot}CH_2)_2TeI_2$, giving a substance offering many possibilities of ring-closure and having some possible physiological interest owing to its relationship with mustard gas. Even at 80°, however, ethylene was evolved, leaving a black substance of undetermined constitution; since this was readily hydrolysed by hot water to tellurium dioxide, it may have been tellurium di-iododibromide: $2C_2H_4BrI + Te \longrightarrow 2C_2H_4 + TeI_2Br_2$.

Attempts to prepare these ββ′-dihalogen diethyl telluride derivatives by the action of ethylene on tellurium tetrachloride or tetrabromide, in either carbon tetrachloride or hydrochloric (hydrobromic) acid, were equally unsuccessful, although syntheses of the selenium analogues by similar methods are known (Bausor, Gibson, and Pope, J., 1920, 117, 1453; Bell and Gibson, J., 1925, 127, 1877; Riley and Friend, J., 1932, 2342; Frick, *J. Amer. Chem. Soc.*, 1923, 45, 1795; Heath and Semon, *J. Ind. Eng. Chem.*, 1920, 12, 1100).

The reaction of tellurium with methylene iodide has been reported in a brief note by Drew (Newton Friend's "Textbook of Inorganic Chemistry," vol. XI, part IV, p. 186; otherwise unpublished) to give di-iodomethyl telluridi-iodide, $(CH_2I)_2TeI_2$, together with a red, amorphous polymer. Reduction of the di-iodide with aqueous metabisulphite is said to give di-iodomethyl telluride as a yellow crystalline substance polymerising above 75°, and as no other information was available, the reaction was re-investigated, since the telluride might, if obtainable in good yield, be of value for synthetic purposes.

It was soon found that the red polymer mentioned by Drew was always the main product. Consistent yields of di-iodomethyl telluridi-iodide were not obtained when amorphous tellurium was heated with methylene iodide (4—13 mols.) between 110° and 150°; the yield fluctuated irregularly with the conditions from 2% to 14%. The only moderately satisfactory result was obtained by heating tellurium (1 mol.) with methylene iodide (13 mols.) at 80° for 49 hours; the di-iodide was isolated in 30% yield, together with much red polymer. However, an exact repetition of the experiment gave only a 3·5% yield of di-iodide, and a much larger amount of polymer. The cause of these inconsistencies is not clear. The red polymer, which is unusually stable to potassium metabisulphite, has not been completely investigated and its constitution (cf. Drew, *loc. cit.*) remains obscure.

Reduction of the crystalline di-iodide with potassium metabisulphite gave di-iodomethyl telluride in quantitative yield. This substance, although apparently unimolecular (soluble in organic solvents, especially acetone) when freshly prepared, became polymerised and insoluble in acetone in the course of a few hours even at room temperature. It did not change in appearance, nor did its melting point alter; the latter fact is not surprising, since polymerisation is probably very rapid long before the melting point (180—185°) is reached, so that the m. p. of any specimen is that of the polymerised substance. When the freshly prepared monomer is dissolved in acetone, the solution, at first clear, quickly becomes turbid; evaporation of a few drops of the turbid solution on a slide showed a mixture of yellow fibrous needles (monomer) and irregular amorphous particles (polymer). Polymerisation probably takes place by telluronium salt formation between the bivalent tellurium atom and the two iodomethyl groups.

In view of the unsatisfactory properties of this telluride, no attempts were made to use it as an intermediate in the synthesis of ring compounds.

Experimental.

The tellurium micro-analyses were carried out by a new method soon to be published by Mr. J. E. Still.

cyclo*Telluributane Dibromide*.—Finely powdered, crystalline tellurium (2·0 g.), sodium formaldehydesulphoxylate (rongalite) (12 g.), and sodium hydroxide (8·5 g.) in water (75 c.c.) were refluxed in an all-glass apparatus consisting of a round-bottomed flask (500 c.c.) fitted with a reflux condenser, stirrer, and tube through which nitrogen was passed. When the original intense reddish-purple colour (polytelluride) had faded to a pale pink (30 minutes), the mixture was allowed to cool somewhat, and tetramethylene dibromide (4·5 g.; 1·3 mols.) added, and washed in with a little alcohol. Refluxing with vigorous stirring was then continued for 15 minutes; no sodium telluride was then left (as shown by a sample of the liquid remaining colourless on exposure to air). Rather dark-coloured drops of a foul-smelling oil were visible in the liquid; after cooling to room temperature, this was extracted thoroughly with chloroform, and the extracts dried over calcium chloride. A slight excess of bromine was added, and a small orange flocculent precipitate filtered off and rejected. On evaporation of the filtrate to small bulk, *cyclo*telluributane dibromide (3·8 g.; 70%) crystallised in 3 crops. This was twice recrystallised from benzene–light petroleum, giving pale yellow prisms (2·75 g.), m. p. 128—131° (Morgan and Burstall, *loc. cit.*, record m. p. 130°).

cyclo*Telluributane Dichloride*.—This was prepared in the same way, bromine being replaced by a stream of chlorine. The crude dichloride (yield, 71%) formed pure white crystals (2·35 g.), m. p. 112°—113° after recrystallisation from carbon tetrachloride (Morgan and Burstall record m. p. 111—112°).

cyclo*Telluripentane Dibromide*.—The sodium telluride solution was prepared as in the previous experiments; after it had been cooled to about 70°, pentamethylene dichloride (2·8 g.; 1·3 mols.) was added, and the mixture refluxed for 45 minutes. When cold, the oil was extracted with carbon tetrachloride, and the extracts dried over calcium chloride. Addition of a slight excess of bromine precipitated some sticky material. The liquor was decanted, evaporated to small bulk, and cleared from more suspended matter by shaking with norit and filtering. Crude dibromide (2·5 g.) was thrown down from the filtrate on addition of light petroleum; two recrystallisations from this solvent (b. p. 60—80°) gave colourless needles (1·85 g.; 33%), m. p. 106—107° (Morgan and Burgess, *loc. cit.*, record 105—107°).

*cyclo*Telluripentane dichloride was made similarly, chlorine being used instead of bromine. Here also gummy by-products were troublesome, and were removed with norit. The pure dichloride (1·55 g.; 37%) formed fluffy white needles, m. p. 105—106°, from light petroleum (b. p. 60—80°) (Morgan and Burgess report m. p. 106—107°).

cyclo*Telluripentane Di-iodide*.—Amorphous tellurium (1·0 g.) and pentamethylene di-iodide (5·05 g.; 2 mols.) were heated together in an oil-bath at 150° for 7 hours with frequent shaking. Excess of pentamethylene di-iodide was then removed by repeated shaking with light petroleum, and the residue taken up in hot acetone, leaving unchanged tellurium (0·06 g.). On evaporation, the acetone extracts gave the crude di-iodide (2·25 g.; 63%), which was very dark, melted at 115—117°, and appeared to contain excess of iodine, possibly as a periodide. After two recrystallisations from acetone (during which the lachrymatory odour of iodoacetone was observed), it formed orange-brown needles, m. p. 135—136·5° (Morgan and Burgess record m. p. 135—136° for both the forms obtained by them).

1 : 4-*Telluroxan* 1 : 1-*Dichloride* (IV, X = Cl).—A hot solution of sodium telluride was prepared from tellurium (6 g.), rongalite (36 g.), sodium hydroxide (25 g.), and water (210 c.c.); $\beta\beta'$-dichlorodiethyl ether (8·0 g.; 1·5 mols.) in a little alcohol was added, and the mixture refluxed for 1 hour. After cooling to room temperature, the oil was extracted with chloroform, and the extracts dried over powdered calcium chloride. Chlorine was passed (external cooling) into the filtered chloroform solution until the discoloured gum first precipitated became a white, solid, semi-crystalline product. This was collected, mixed with the small crop obtained by evaporating the filtrate to small bulk, and extracted exhaustively with boiling acetone. The residue (*ca.* 4 g.) was a white, amorphous, insoluble substance which could not be crystallised, and was not further examined. On evaporation of the acetone solution, almost pure telluroxan dichloride was collected (5·9 g.; 46%). Two other similar experiments each gave 44·5% yields.

On two occasions, carbon tetrachloride was used instead of chloroform for extraction; in these cases the discoloured gum formed on chlorination did not alter on continued passage of chlorine, but on extraction with acetone the yield was very similar (40%, 47%), the insoluble residue being grey or black. A close search of the chloroform and acetone mother-liquors from these syntheses disclosed a further 3% of telluroxan dichloride but no other crystalline material.

Telluroxan dichloride crystallises from acetone in white plates, m. p. 179·5° (some decomp.) (Found: Cl, 26·2; Te, 46·6. $C_4H_8OCl_2Te$ requires Cl, 26·2; Te, 47·1%). It is moderately readily soluble in cold acetone, can be crystallised from boiling alcohol, but is very sparingly soluble in benzene, carbon tetrachloride and chloroform and insoluble in light petroleum. It is dissolved by boiling with water for some minutes, giving an acid solution which deposits a scanty amorphous white precipitate on cooling.

Telluroxan dibromide (IV, X = Br) was prepared in exactly the same way, bromine being substituted for chlorine. It separated from acetone in glittering platelets of a very pale yellow tinge, m. p. 157—158° (decomp.). Its properties and solubilities are similar to those of the dichloride (Found: Br, 43·5; Te, 35·4. $C_4H_8OBr_2Te$ requires Br, 44·5; Te, 35·5%).

Telluroxan Dihydroxide (IV, X = OH).—Telluroxan dichloride (2 g.) was ground in a glass mortar with a little water and silver oxide, prepared from silver nitrate (3 g.). After one hour the silver compounds were filtered off, and the filtrate evaporated to dryness under reduced pressure. The light grey residue was taken up in hot alcohol (10 c.c.), and the solution stirred with norit and filtered. The clear filtrate was evaporated in a vacuum desiccator, leaving the *dihydroxide* as a faintly discoloured, very deliquescent, waxy mass of radiating needles, freely soluble in water to give an alkaline solution (Found: Te, 53·3. $C_4H_{10}O_2Te$ requires Te, 54·6%). Accurate analytical figures were not obtained, owing to the hygroscopic nature of this substance.

The following four substances were prepared from the aqueous solution of the dihydroxide, made as described above.

Telluroxan Hydroxy-nitrate (VI, X = NO_3).—On the addition of a few drops of nitric acid a crop of heavy white crystals separated. After cooling to 0°, these were collected, and recrystallised from a small volume of water; yield, 0·4 g. from 1 g. of dichloride. The *hydroxy-nitrate* consists of short rods pointed at both ends, m. p. 190° (vigorous efferv.) (Found: N, 5·0; Te, 44·8. $C_4H_9O_5NTe$ requires N, 5·0; Te, 45·8%). It is rather soluble in water, and explodes feebly when heated in the free flame.

Telluroxan Hydroxy-picrate [VI, X = $C_6H_2(NO_2)_3O$].—Addition of hot aqueous picric acid solution formed a yellow precipitate, which was twice recrystallised from boiling water, giving radiating clusters of brilliant yellow needles, m. p. 238° (efferv.) after blackening above 210° (Found: N, 9·5, 9·5; Te, 28·6, 28·5. $C_{10}H_{11}O_9N_3Te$ requires N, 9·5; Te, 28·7%). Yield, 1·1 g. from 1 g. of the dichloride.

Telluroxan Hydroxy-picrolonate (VI, X = $C_{10}H_7O_5N_4$).—This was made in a similar manner, and recrystallised from a large bulk of hot water, in which it was rather sparingly soluble. It formed stellate clusters of thin rods, paler yellow than the picrate, m. p. 216° (violent efferv.) after darkening above 150° (Found: N, 11·5; Te, 26·5. $C_{14}H_{16}O_7N_4Te$ requires N, 11·7; Te, 26·6%).

Telluroxan Di-iodide (IV, X = I).—Neutralisation of the dihydroxide solution with dilute hydriodic acid gave a red

crystalline precipitate of the *di-iodide*, which crystallised from acetone in large, bright red prisms, m. p. 155° (decomp.) (Found: Te, 28·0. $C_4H_8OI_2Te$ requires Te, 28·1%). In solvents other than acetone it is rather sparingly soluble.

Other Reactions of Telluroxan Dihydroxide Solution.—Hydrochloric and hydrobromic acids gave immediate crystalline precipitates of the dihalide. Sulphuric, hydrofluoric, acetic, formic, oxalic, perchloric and chromic acids gave no precipitates; the perchlorate was isolated as a mass of white needles by evaporation on the steam-bath, but it was very hygroscopic and analytical results were poor.

1 : 4-*Telluroxan* (III).—Telluroxan dichloride (10 g.), potassium metabisulphite (17 g.), water (100 c.c.), and carbon tetrachloride (50 c.c.) were shaken together in a separating funnel until all but a trace of solid had disappeared. The carbon tetrachloride layer was removed, the aqueous layer extracted twice more, and the mixed extracts dried over calcium chloride. It was then necessary to leave the solution overnight, during which time a brown, varnish-like film was deposited on the walls of the flask. Most of the solvent was next removed on the water-bath, considerable deposition of amorphous polymer occurring during the process. The residue was distilled under reduced pressure in an all-glass apparatus, nitrogen being passed through the capillary. After removal of residual solvent, telluroxan (*ca.* 6 g.) passed over as a lemon-yellow oil, b. p. 90°/21 mm., with a nauseating and moderately persistent odour. Owing to this unpleasant property, not as many experiments were made as would otherwise have seemed desirable. When supercooled at 0° to −5°, telluroxan crystallised and then had m. p. 6°; the initial solidification necessitated cooling to −40°. It had $n^{18°}$ 1·6340 for white light and $d^{20°}$ 1·8, and was miscible with the usual organic solvents but insoluble in water (Found: C, 24·0; H, 4·3; Te, 63·8. C_4H_8OTe requires C, 24·0; H, 4·0; Te, 63·9%). Although the solution of crude telluroxan in carbon tetrachloride seemed so unstable, the pure liquid showed no particular tendency to change, and could be kept for at least 18 months in sealed tubes in the dark. As expected, it gave immediate precipitates of dihalides when treated with bromine in carbon tetrachloride or iodine in alcohol. When a few drops were left exposed to the air for 36 hours, the liquid partly evaporated and was partly converted into the sticky crystalline dihydroxide.

Telluroxan Methiodide (V).—On addition of excess of methyl iodide to an acetone solution of telluroxan, the *methiodide* soon began to separate; it was recrystallised by suspending it in boiling alcohol, adding water until it dissolved, stirring in a little norit, filtering and cooling. It formed extremely pale yellow needles, m. p. 199° (efferv.), after becoming brown above 120°; it was easily soluble in water, sparingly in alcohol and acetone (Found: C, 17·7; H, 3·5; Te, 37·1. $C_5H_{11}OITe$ requires C, 17·6; H, 3·2; Te, 37·4%).

Di-iodomethyl Telluridi-iodide.—Only the most successful preparation is described. Amorphous tellurium (1 g.) and methylene iodide (26 g.) were heated at 80° for 49 hours. The excess of methylene iodide was removed under reduced pressure, and the residue extracted exhaustively with boiling alcohol. The alcoholic liquors yielded crude di-iodide (1·55 g.; 30%); the residue (1·5 g.) was a mixture of tellurium and red polymer. *Di-iodomethyl telluridi-iodide* crystallised from alcohol or acetone in dark red, irregular crystals, m. p. 127°, very sparingly soluble in other solvents (Found: C, 3·6; H, 0·7; Te, 19·5. $C_2H_4I_4Te$ requires C, 3·6; H, 0·6; Te, 19·2%).

Di-iodomethyl Telluride.—The di-iodide (1·12 g.) was ground for 20 minutes with potassium metabisulphite (1·1 g.; 3 mols.) and a little water. The yellow solid was collected and dried in a vacuum desiccator; yield, 0·69 g. (quantitative). On heating, it became orange above *ca.* 80°, softened about 155°, and melted with blackening and intumescence at 180–185° (Found: Te, 31·2. $C_2H_4I_2Te$ requires Te, 31·2%).

Our thanks are due to Mr. J. E. Still for the microanalyses, and to the Department of Scientific and Industrial Research for a maintenance grant to one of us (W. V. F.).

UNIVERSITY COLLEGE, NOTTINGHAM. [*Received, September 9th,* 1944.]

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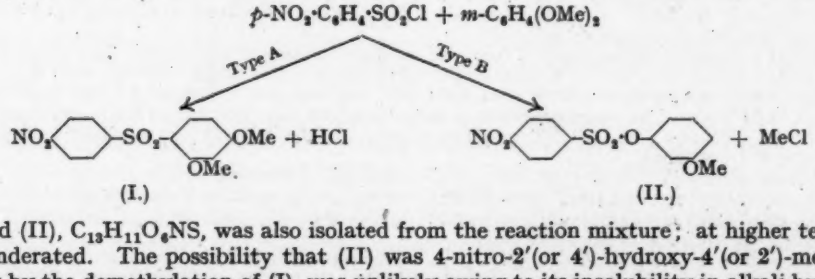
5. *The Reaction between Sulphonyl Chlorides and Dimethoxybenzenes in the Presence of Zinc Chloride.*

By HAROLD BURTON and ERIC HOGGARTH.

Alkyl- and aryl-sulphonyl chlorides react with the dimethoxybenzenes in the presence of zinc chloride, giving the corresponding anisyl alkyl- and aryl-sulphonates and, in some cases, the dimethoxyphenylaryl-sulphones. In general, formation of the sulphonate is favoured by the *o*- and *p*-dimethoxybenzenes and by the more reactive sulphonyl chlorides.

THE preparation of a series of diaryl- and arylalkyl-sulphones containing hydroxyl, methoxyl, and amino-groups was undertaken in order that the antibacterial activities of compounds related to the very active 4 : 4′-diaminodiphenylsulphone might be determined. It was discovered that *p*-nitrobenzenesulphonyl chloride and resorcinol dimethyl ether reacted vigorously in the presence of zinc chloride at 125°, and the main product was proved by independent synthesis to be 4-*nitro*-2′ : 4′-*dimethoxydiphenylsulphone* (I) (Type A). A

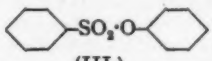


(I.) (II.)

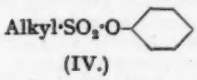
second compound (II), $C_{13}H_{11}O_6NS$, was also isolated from the reaction mixture; at higher temperatures this substance preponderated. The possibility that (II) was 4-nitro-2′(or 4′)-hydroxy-4′(or 2′)-methoxydiphenyl-sulphone, arising by the demethylation of (I), was unlikely owing to its insolubility in alkali hydroxide. After it had been established that methyl chloride was liberated during the reaction, it appeared certain that (II) was actually m-*amisyl* p-*nitrobenzenesulphonate* (Type B); this was confirmed by independent synthesis.

The scope of the method was then assessed by investigating the reaction between the three dimethoxybenzenes and various alkyl- and aryl-sulphonyl chlorides. In general, type B reaction is more common than type A, particularly with the alkylsulphonyl chlorides: but in some cases, as above and with, for example, veratrole and arylsulphonyl chlorides, both types occur simultaneously. The point of attack in the dimethoxybenzene molecule thus seems to depend on the nature of both the sulphonyl chloride and the dimethoxybenzene; no true generalisation has been found possible.

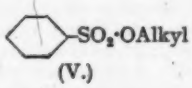
The case of 3-methyl-*n*-butanesulphonyl chloride and the dimethoxybenzenes was complicated by the difficulty of characterising the oily products; the sulphones were therefore demethylated, and the crystalline hydroxy-compounds obtained. Unexpectedly it was found that the sulphonates were sufficiently stable to be demethylated by boiling 46% hydrobromic acid and it was thus possible to prepare corresponding crystalline compounds from them also. Alkali, however, hydrolysed the sulphonates to the corresponding phenols and this was used as additional proof of constitutions. It is remarkable that sulphonates of types (III) and (IV) are stable, whereas an example of type (V) is reported by Walter (*J. Amer. Chem. Soc.*, 1943, **65**, 739) to be very unstable.



(III.)



(IV.)



(V.)

It has been observed that a number of compounds of type (III) containing nitro-groups are strongly discoloured on standing in the light.

The reactions were carried out in an apparatus similar to that used for methoxy-determinations by Zeisel's method, and the liberated methyl chloride collected in a trap, cooled in solid carbon dioxide and ethyl alcohol. In instances where type A reactions preponderated, a little methyl chloride was condensed but much hydrogen chloride was found in the effluent gas. In examples of type B reactions the amount of methyl chloride corresponded to 60—75% of the theoretical and in those cases in which both sulphonate and sulphone were isolated the amount of methyl chloride was roughly proportional to the amount of sulphonate. No reaction was detected when the dimethoxybenzenes were heated with zinc chloride alone, or with the sulphonyl chlorides alone, and the starting materials were recovered unchanged in all instances after prolonged heating at 20—30° above the usual reaction temperature.

The compounds were tested for antibacterial activity by Dr. Martin of the Biological Department, Imperial Chemical Industries Limited, Blackley. No high degree of activity was found in any instance.

Experimental.

I. *Reactions with Arylsulphonyl Chlorides.*

4-Nitro-2′ : 4′-dimethoxydiphenylsulphone (I).—(*a*) *p*-Nitrobenzenesulphonyl chloride (44 g.) and resorcinol dimethyl ether (28 g.) were melted together, freshly crushed zinc chloride (41 g.) added, and the mixture slowly heated in a slow stream of dry nitrogen. At 98° (internal temperature) a deep red coloration was observed, at 106° some hydrogen chloride escaped, and at 125° evolution of gas was rapid. Heating was continued for 30 mins. at 125°, during which time a small amount of methyl chloride (0·8 g.) was condensed in the solid carbon dioxide trap. The reaction mixture was cooled and extracted with boiling benzene (500 c.c.), and the extract washed with 5% sodium hydroxide solution, then with water, and evaporated. *4-Nitro-2′ : 4′-dimethoxydiphenylsulphone* crystallised from β-ethoxyethyl alcohol in colourless prisms, m. p. 183° (7·8 g.; 12·0%) (Found: C, 51·6; H, 3·8. $C_{14}H_{13}O_6NS$ reuires C, 52·0; H, 4·0%).

(*b*) To a solution of sodium (0·25 g.) in absolute ethyl alcohol (100 c.c.) was added 2 : 4-dimethoxythiophenol (1·7 g.), followed by *p*-chloronitrobenzene (1·7 g.), and the mixture refluxed for 3 hours. Water (150 c.c.) was added, and the solid collected, washed with water, and crystallised from ethyl alcohol, giving lustrous needles of *4-nitro-2′ : 4′-dimethoxydiphenyl sulphide* (2·1 g.; 75·6%), m. p. 126° (Found: C, 57·7; H, 4·0. $C_{14}H_{13}O_4NS$ requires C, 57·7; H, 4·4%). This sulphide (2·0 g.) in acetic acid (10 c.c.) was heated to boiling under reflux, and 30% hydrogen peroxide (3·0 c.c.) added. When the reaction subsided, the solution was warmed on the water-bath for 1 hr. and diluted with water (300 c.c.), and the solid collected. From ethyl alcohol, colourless plates, m. p. 183°, undepressed by admixture with the compound obtained under (*a*), were obtained (1·8 g.; 81·1%) (Found: C, 51·7; H, 4·1%).

4-Amino-2′ : 4′-dimethoxydiphenylsulphone.—The above sulphone (6·5 g.) was reduced with hydrogen in presence of Raney nickel (absorption, corrected to N.T.P., 1375 c.c. Calc., 1352 c.c.). The filtered solution was evaporated; the residue crystallised from ethyl alcohol in long colourless needles (4·5 g.; 76·8%), m. p. 196—198° (Found: C, 57·05; H, 5·0. $C_{14}H_{15}O_4NS$ requires C, 57·3; H, 5·2%).

m-*Anisyl* p-*Nitrobenzenesulphonate* (II).—(*a*) When *p*-nitrobenzenesulphonyl chloride (22 g.), resorcinol dimethyl ether (14 g.), and zinc chloride (41 g.) were quickly heated in an oil-bath at 135—140°, a vigorous reaction with much charring took place. The *ester*, isolated as described under (I) (*a*), had m. p. 109° (from β-ethoxyethyl alcohol, in which it was markedly more soluble than 4-nitro-2′ : 4′-dimethoxydiphenylsulphone) (3·2 g.; 10·3%) (Found: C, 50·6; H, 3·75; N, 4·45. $C_{13}H_{11}O_6NS$ requires C, 50·5; H, 3·6; N, 4·5%). This compound (1·5 g.) was refluxed with potassium hydroxide (0·8 g.) in water (15 c.c.) and dioxan (5 c.c.) for 5 hours, the clear liquid evaporated under reduced pressure, the residue dissolved in water (30 c.c.), filtered (charcoal), and made acid to Congo-red paper (concentrated hydrochloric acid), and the oil extracted with ether. The residue left on evaporation of the dried extracts was distilled, giving a colourless oil (0·5 g.; 80%), b. p. 120—125°/15 mm., which was identified by conversion into 2 : 4 : 6-tribromo-3-methoxyphenol, m. p. 103°, not depressed by an authentic sample.

(*b*) A solution of resorcinol monomethyl ether (6·2 g.) in dry pyridine (30 c.c.) was shaken with *p*-nitrobenzenesulphonyl chloride (11·1 g.). The mixture, which became warm (70—75°), was kept overnight and then treated with water (100 c.c.), and the solid collected and washed with water. From β-ethoxyethyl alcohol, colourless prisms, m. p. 109°, not depressed by the compound from (*a*), were obtained (8·2 g.; 52·6%) (Found: C, 50·8; H, 3·7%).

m-*Anisyl Sulphanilate.*—The nitrobenzenesulphonate (3·1 g.) was reduced (hydrogen and Raney nickel catalyst; absorption, reduced to N.T.P., 720 c.c.; calc., 672 c.c.). The *amino*-compound crystallised from benzene–light petroleum (b. p. 60—80°) in colourless prisms (2·2 g.; 78·8%), m. p. 37—38° (Found: C, 56·2; H, 5·05. $C_{13}H_{13}O_4NS$ requires C, 55·9; H, 4·7%).

p-*Anisyl* p-*Nitrobenzenesulphonate*.—The reaction between quinol dimethyl ether and *p*-nitrobenzenesulphonyl chloride in the presence of zinc chloride as described above gave as the principal isolated product this *ester* (15·5%), m. 153—154° (colourless prisms from ethyl alcohol). Methyl chloride (55% of the theoretical amount) was also obtained. By the reaction between quinol monomethyl ether and *p*-nitrobenzenesulphonyl chloride in pyridine solution, the same compound was obtained (59%), m. p. 153—154°, not depressed by the compound obtained by the first route (Found: S, 10·4. $C_{13}H_{11}O_6NS$ requires S, 10·35%).

p-*Anisyl Sulphanilate*.—The above compound (3·1 g.) was reduced in methyl alcohol with Raney nickel (absorption 650 c.c., calc. 672 c.c., at N.T.P.), and the filtered solution concentrated. The *amino*-compound separated, on cooling, in colourless needles (2·4 g.; 86%), m. p. 168° (Found: C, 56·05; H, 4·75%).

o-*Anisyl* p-*Nitrobenzenesulphonate*.—Veratrole and *p*-nitrobenzenesulphonyl chloride, in the presence of zinc chloride, gave as the main isolated product this *ester* (15·6%), m. p. 112° (from ethyl alcohol). Methyl chloride (58%) was also obtained. Reaction of guaiacol and *p*-nitrobenzenesulphonyl chloride in pyridine gave the same compound (88%), m. p. 112°, not depressed by the compound obtained by the first route (Found: S, 10·1 $C_{13}H_{11}O_6NS$ requires S, 10·35%).

o-*Anisyl Sulphanilate*.—The above nitro-compound was reduced in the usual manner (76·1%); the *amine* crystallised from methyl alcohol (in which it was very soluble) in colourless prisms, m. p. 141—142° (Found: C, 55·5; H, 4·75%).

Reaction of m-*Nitrobenzenesulphonyl Chloride with Dimethoxybenzenes*.—In these cases the only product isolated was the sulphonate and identity of the product with that prepared from the monomethyl ether of the corresponding dihydroxybenzene was established by mixed m. p. and by reduction to identical amino-compounds: p-*Anisyl* m-*nitrobenzenesulphonate*, m. p. 91—92° (Found: C, 50·9; H, 3·8; S, 10·1%); p-*anisyl* m-*aminobenzenesulphonate*, m. p. 62° (Found: C, 55·4; H, 4·3%). m-*Anisyl* m-*nitrobenzenesulphonate*, m. p. 71—72° (Found: C, 50·65; H, 3·9%); m-*anisyl* m-*aminobenzenesulphonate*, oil (Found: C, 56·3; H, 5·15%) [*acetyl* derivative, m. p. 87° (Found: N, 4·5; S, 9·85. $C_{15}H_{15}O_5NS$ requires N, 4·4; S, 10·0%)]. o-*Anisyl* m-*nitrobenzenesulphonate*, m. p. 84° (Found: C, 50·3; H, 3·55; S, 10·15%); o-*anisyl* m-*aminobenenzesulphonate*, m. p. 110° (Found: C, 55·75; H, 4·5%).

2 : 4 : 4′-*Trimethoxydiphenylsulphone*.—Anisole-*p*-sulphonyl chloride (10·3 g.), resorcinol dimethyl ether (6·9 g.), and zinc chloride (6·8 g.) reacted at 110° with evolution of much hydrogen chloride but only a trace of methyl chloride. The product was extracted several times with chloroform–ether, and the extracts evaporated to 200 c.c., filtered, washed successively with dilute hydrochloric acid, water, dilute sodium hydroxide solution, and water, and evaporated. The residue crystallised from methyl alcohol in colourless prisms (8·2 g.; 53·2%), m. p. 118°. Repeated crystallisation from methyl alcohol raised the m. p. to 123° (Found: C, 58·2; H, 5·2; S, 10·6. $C_{15}H_{16}O_5S$ requires C, 58·4; H, 5·2; S 10·4%).

m-*Anisyl* p-*Methoxybenzenesulphonate*.—The sulphonyl chloride reacted with resorcinol monomethyl ether in pyridine solution to give the *ester*, b. p. 200—202°/0·5 mm., $n_D^{20°}$ 1·5731, which slowly set to a crystalline solid; this, recrystallised from methyl alcohol, formed colourless prisms (88%), m. p. 52° (Found: C, 56·9; H, 4·6. $C_{14}H_{14}O_5S$ requires C, 57·15; H, 4·8%).

4-*Chloro*-2′: 4′-*dimethoxydiphenylsulphone*.—This *compound*, obtained in 54·6% yield by interaction of *p*-chlorobenzenesulphonyl chloride and resorcinol dimethyl ether as described under 2 : 4 : 4′-trimethoxydiphenylsulphone, crystallised from alcohol in colourless prisms, m. p. 166° (Found: C, 54·1; H, 4·25. $C_{14}H_{13}O_4ClS$ requires C, 53·75; H, 4·2%).

m-*Anisyl* p-*Chlorobenzenesulphonate*.—*p*-Chlorobenzenesulphonyl chloride and resorcinol monomethyl ether reacted in pyridine solution to give the *ester* (58%), b. p. 190—191°/0·5 mm., $n_D^{20°}$ 1·5788, which did not solidify (Found: C, 52·2; H, 3·8. $C_{13}H_{11}O_4ClS$ requires C, 52·3; H, 3·7%).

2 : 4-*Dimethoxydiphenylsulphone*, obtained from benzenesulphonyl chloride and resorcinol dimethyl ether by the procedure given under 2 : 4 : 4′-trimethoxydiphenylsulphone, formed colourless prisms (44%), m. p. 121—122°, from ethyl alcohol (Found: C, 60·5; H, 5·2; S, 11·6. $C_{14}H_{14}O_4S$ requires C, 60·4; H, 5·0; S, 11·5%). Demethylation with 46% hydrobromic acid gave 2 : 4-dihydroxydiphenylsulphone, m. p. 121° (U.S.P. 2,288,282; *Chem. Abs.*, 1943, **37**, 141, gives m. p. 115—116°) (Found: C, 54·25, 53·7; H, 4·4, 4·1. Calc. for $C_{12}H_{10}O_4S,H_2O$: C, 53·7; H, 4·5%).

m-*Anisyl benzenesulphonate*, obtained from resorcinol monomethyl ether and benzenesulphonyl chloride, was a colourless oil, b. p. 188—190°/1·0 mm., $n_D^{20°}$ 1·5636 (Found: S, 12·0. $C_{13}H_{12}O_4S$ requires S, 12·1%).

Reaction of Benzenesulphonyl Chloride and Toluene-p-*sulphonyl Chloride with Veratrole*.—Two compounds were formed in each case and by comparison with the sulphonates obtained from guaiacol in pyridine solution one member of each pair was identified as the *o*-anisyl arylsulphonate. The excluded member of each pair is regarded by analogy as the 3 : 4-dimethoxy-sulphone. In the case of 3 : 4-dimethoxydiphenylsulphone the reaction mixture was best hydrolysed with alkali hydroxide, and the sulphone then extracted with chloroform. The following were obtained: 3 : 4-*Dimethoxydiphenylsulphone*, m. p. 118—119° (Found: C, 60·5; H, 5·2. $C_{14}H_{14}O_4S$ requires C, 60·4; H, 5·0%). o-*Anisyl benzenesulphonate*, m. p. 51—52° (Found: C, 59·15; H, 4·8. $C_{13}H_{12}O_4S$ requires C, 59·1; H, 4·5%). 3 : 4-*Dimethoxy*-4′-*methyldiphenylsulphone*, m. p. 130—131° (Found: C, 61·4; H, 5·5. $C_{15}H_{16}O_4S$ requires C, 61·6; H, 5·5%). o-*Anisyl* p-*toluenesulphonate*, m. p. 85—86° (Found: C, 60·5; H, 4·65. $C_{14}H_{14}O_4S$ requires C, 60·4; H, 5·0%).

Reaction between *o*-nitrobenzenesulphonyl chloride and the dimethoxybenzenes proceeded in an uncontrolled manner and charred products were obtained.

II. *Reactions with Alkylsulphonyl Chlorides.*

p-*Anisyl* 3-*Methyl*-n-*butanesulphonate*.—(*a*) Quinol dimethyl ether (6·9 g.), 3-methyl-*n*-butanesulphonyl chloride (8·6 g.), and anhydrous zinc chloride (6·8 g.) were heated slowly in a stream of dry nitrogen. At 92° (internal temperature) a blue coloration was observed, at 102° some methyl chloride condensed in the solid carbon dioxide trap, and at 125° condensation of methyl chloride was rapid and continued for about 15 mins. After being heated for a further 15 mins. at 125°, the mixture was cooled and dissolved in ether (400 c.c.). The solution was shaken successively with dilute hydrochloric acid (20 c.c. of conc. acid and 100 c.c. of water), water, 5% sodium hydroxide solution, and water, dried, and evaporated. The residue was distilled, giving a main fraction (7·5 g.; 58·1%), b. p. 150—155°/0·1 mm., which on redistillation gave a colourless oil, b. p. 150—151°/0·1 mm., $n_D^{20°}$ 1·5112 (Found: C, 56·1; H, 7·2. $C_{12}H_{18}O_4S$ requires C, 55·8; H, 7·0%). The yield of methyl chloride was 1·8 g. (71·3%), but no fuming due to hydrogen chloride was noticed. The above sulphonate (2·6 g.) was boiled with sodium hydroxide (1 g.) in water (15 c.c.) and dioxan (5 c.c.) for 7 hrs., the clear liquid evaporated under reduced pressure, and the residue dissolved in water (30 c.c.), filtered (charcoal), made acid (Congo-red) (concentrated hydrochloric acid), and extracted with ether. Distillation gave a colourless oil, b. p. 120—130°/15 mm., setting to a mass of colourless crystals (1·1 g.; 88·7%), m. p. 48°. Plates were obtained from light petroleum containing a little ethyl acetate, m. p. 53°, not depressed by authentic quinol monomethyl ether.

(*b*) A solution of quinol monomethyl ether (15·5 g.) in dry pyridine (20 c.c.) was treated with 3-methyl-*n*-butanesulphonyl chloride (21·3 g.) and kept for 24 hours. The mixture was ground with water (100 c.c.), concentrated hydrochloric acid added (Congo-red), the oil extracted with carbon tetrachloride, and the extract washed with 10% sodium

hydroxide solution, then with water, and evaporated. Distillation gave a colourless oil (24 g.; 74·5%), b. p. 148—150°/0·1 mm., $n_D^{20°}$ 1·5109 (Found: C, 55·95; H, 7·3%). Hydrolysis as described under (*a*) gave quinol monomethyl ether (80%).

p-*Hydroxyphenyl* 3-*Methyl*-n-*butanesulphonate*.—*p*-Anisyl 3-methyl-*n*-butanesulphonate (5·2 g.) was heated with 48% hydrobromic acid (50 c.c.) just below the b. p. with mechanical stirring for 16 hours. The liquid was cooled, and ice (200 g.) added, followed by 30% sodium hydroxide solution (70 c.c.). The alkaline solution was extracted several times with small amounts of benzene, and the aqueous layer stirred with charcoal, filtered, and made acid to Congo-red paper with concentrated hydrochloric acid. The liberated p-*hydroxyphenyl* ester was extracted with benzene, dried, and distilled, giving a pale yellow oil, b. p. 185—188°/0·5 mm., $n_D^{20°}$ 1·5220 (Found: C, 53·9; H, 6·7. $C_{11}H_{16}O_4S$ requires C, 54·1; H, 6·6%).

Hydrolysis of this compound (1·1 g.) gave quinol (0·3 g.), m. p. 166—168°, which was converted into its diacetate, plates from dilute acetic acid, m. p. 121°, not depressed by an authentic sample.

Acetylation of the *p*-hydroxylphenyl ester (0·75 g.) with acetic anhydride (3 c.c.) and 1 drop of concentrated sulphuric acid gave p-*acetoxyphenyl* 3-*methyl*-n-*butanesulphonate*, which, crystallised from light petroleum, gave colourless plates (0·3 g.), m. p. 48° (Found: C, 54·2; H, 6·5. $C_{13}H_{18}O_5S$ requires C, 54·5; H, 6·3%).

Quinol Bis-3-*methyl*-n-*butanesulphonate*.—The *p*-hydroxyphenyl ester (2·4 g.) in pyridine (2 c.c.) was treated with 3-methyl-*n*-butanesulphonyl chloride (1·7 g.). After 48 hrs., the mixture was treated with water (100 c.c.), and the solid collected and crystallised from methyl alcohol, giving colourless prisms (2·0 g.; 53%), m. p. 61° (Found: C, 50·5; H, 6·8. $C_{16}H_{26}O_6S_2$ requires C, 50·8; H, 6·9%).

Quinol (11 g.) in pyridine (30 c.c.) was treated (stirring) with 3-methyl-*n*-butanesulphonyl chloride (34 g.), the temperature being controlled by external cooling (ice). After 18 hours, the mixture was treated with water (200 c.c.) and made strongly alkaline with 20% sodium hydroxide solution. Quinol bis-3-methyl-*n*-butanesulphonate was collected, washed with water, and crystallised from methyl alcohol, giving large colourless plates (10·1 g.; 26·7%), m. p. 61°. The alkaline filtrate was acidified (hydrochloric acid), the oil extracted with carbon tetrachloride, and the solvent evaporated. The residual oil was distilled, giving a small amount of unchanged quinol and a main fraction, b. p. 175—185°/0·5 mm., from which was obtained by redistillation pure *p*-hydroxyphenyl 3-methyl-*n*-butanesulphonate (6·3 g.; 25·8%), b. p. 180—182°/0·5 mm., $n_D^{20°}$ 1·5219 (Found: C, 54·4; H, 6·7%). The acetoxy-compound prepared from this had m. p. 48°, undepressed by specimens prepared by the other methods.

2 : 5-*Dimethoxythiophenol*.—This *compound* was prepared by Suter and Johnson's method (*J. Amer. Chem. Soc.*, 1932, **54**, 4102), in 48% yield, as a colourless oil, b. p. 138—140°/20 mm., $n_D^{20°}$ 1·5848 (Found: S, 18·7. $C_8H_{10}O_2S$ requires S, 18·8%).

2 : 5-*Dimethoxyphenyl* iso*Amyl Sulphide*.—Sodium (2·8 g.) in absolute ethyl alcohol was treated with the above thiophenol (17 g.), and *iso*amyl bromide (18 g.) added down a reflux condenser with shaking. A vigorous reaction took place which was completed on the steam-bath (3 hrs.). The mixture was diluted with water and ice, and the solid collected and washed with ice-water (yield, 21 g.; 87·5%). A small specimen was distilled, b. p. 153—155°/0·5 mm., and set to a crystalline mass, m. p. 31—33° (Found: S, 13·5. $C_{13}H_{20}O_2S$ requires S, 13·3%).

2 : 5-*Dimethoxyphenyl*iso*amylsulphone*.—The crude sulphide (20 g.) was dissolved in boiling acetic acid (75 c.c.), and 30% hydrogen peroxide (45 c.c.) added down a long reflux condenser. The reaction, at first violent, was completed on the steam-bath (2 hrs.), the liquor diluted with water (200 c.c.), and the oil extracted with benzene. The residue left after evaporation of the solvent was distilled, b. p. 198—198·5°/0·8 mm., $n_D^{20°}$ 1·5290 (17·1 g.; 79·2%) (Found: C, 57·15; H, 7·1. $C_{13}H_{20}O_4S$ requires C, 57·35; H, 7·35%).

2 : 5-*Dihydroxyphenyl*iso*amylsulphone*.—The methoxy-sulphone (5·4 g.) and 46% hydrobromic acid (50 c.c.) were refluxed with stirring for 12 hours. The liquid was cooled (ice-salt bath) and stirred whilst concentrated sodium hydroxide solution was run in until alkaline (Clayton-yellow). The alkaline solution was extracted several times with carbon tetrachloride, cleared with charcoal, and made strongly acid (concentrated hydrochloric acid), and the oil extracted with benzene. The residue left on evaporation of the solvent was distilled, giving a pale yellow liquid, b. p. 195—196°/0·8 mm., $n_D^{20°}$ 1·5499, which solidified on long standing to a crystalline mass (3·6 g.; 53·8%), m. p. 56° (Found: C, 53·8; H, 6·5. $C_{11}H_{16}O_4S$ requires C, 54·1; H, 6·6%). Acetylation with acetic anhydride and 1 drop of concentrated sulphuric acid gave colourless prisms of the *diacetate*, m. p. 97° (Found: C, 54·1; H, 6·1. $C_{15}H_{20}O_6S$ requires C, 54·9; H, 6·1%).

m-*Anisyl* 3-*Methyl*-n-*butanesulphonate*.—The reaction between 3-methyl-*n*-butanesulphonyl chloride and resorcinol dimethyl ether in the presence of zinc chloride gave m-*anisyl* 3-*methyl*-n-*butanesulphonate* (63·2%), b. p. 178—180°/0·1 mm., $n_D^{20°}$ 1·5119 (Found: C, 55·7; H, 6·7. $C_{12}H_{18}O_4S$ requires C, 55·8; H, 7·0%). Methyl chloride (75%) was collected, and a deep red colour was produced in the reaction mixture.

The same compound was obtained (47%) from resorcinol monomethyl ether and 3-methyl-*n*-butanesulphonyl chloride in the presence of pyridine, b. p. 157—158°/0·05 mm., $n_D^{20°}$ 1·5117 (Found: C, 56·05; H, 7·15%).

Both specimens of this compound were hydrolysed to resorcinol monomethyl ether, identified as its 2 : 4 : 6-tribromo-derivative, m. p. 103°.

m-*Hydroxyphenyl* 3-*Methyl*-n-*butanesulphonate*.—This *compound*, obtained by demethylation of the *m*-anisyl ester as described under the *p*-hydroxy-ester, had b. p. 165—167°/0·1 mm., m. p. 48—50° (Found: C, 54·0, 54·5; H, 6·7, 6·6. $C_{11}H_{16}O_4S$ requires C, 54·1; H, 6·6%). The same compound was obtained (55%) by treating resorcinol with 3-methyl-*n*-butanesulphonyl chloride (1 mol.) in pyridine and had m. p. 48—50°, not depressed by specimens obtained by the former methods. Hydrolysis gave resorcinol (66%), identified by mixed m. p.

2 : 4-*Dimethoxyphenyl*iso*amylsulphone*.—This *compound*, prepared from 2 : 4-dimethoxythiophenol as described under 2 : 5-dimethoxyphenyl*iso*amylsulphone, had b. p. 172—173°/0·1 mm., $n_D^{20°}$ 1·5508 (Found: C, 57·85; H, 7·2. $C_{13}H_{20}O_4S$ requires C, 57·35; H, 7·35%).

p-*Anisyl Methanesulphonate*.—(*a*) Quinol dimethyl ether (6·9 g.) and methanesulphonyl chloride (5·8 g.) reacted in the presence of zinc chloride (13·6 g.) to give methyl chloride (1·4 g.; 56%) and p-*anisyl methanesulphonate*, b. p. 180—185°/25 mm., crystallising in colourless prisms from aqueous ethyl alcohol, m. p. 79—80° (3·7 g.; 55·2%) (Found: C, 47·2; H, 5·15. $C_8H_{10}O_4S$ requires C, 47·5; H, 4·95%).

(*b*) Quinol monomethyl ether (6·2 g.) and methanesulphonyl chloride (6·3 g.) in pyridine (10 c.c.) gave colourless prisms (7·0 g.; 69%), m. p. 79—80°, not depressed by the compound prepared as in (*a*).

p-*Hydroxyphenyl Methanesulphonate*.—*p*-Anisyl methanesulphonate (4·0 g.) was demethylated by 46% hydrobromic acid (40 c.c.) as described for the 3-methyl-*n*-butanesulphonate, giving a colourless oil (3·2 g.; 66·5%), b. p. 172—174°/0·5 mm., which solidified to a crystalline mass, m. p. 68—70°. From benzene–light petroleum, colourless prisms, m. p. 73°, were obtained (Found: C, 44·5; H, 4·1. $C_7H_8O_4S$ requires C, 44·7; H, 4·3%).

Quinol Bismethanesulphonate.—*p*-Hydroxyphenyl methanesulphonate (1·9 g.) in pyridine (6 c.c.) with methanesulphonyl chloride (1·3 g.) gave colourless needles (1·65 g.; 62%), from ethyl alcohol, m. p. 168° (Found: C, 35·8; H, 3·6. $C_8H_{10}O_6S_2$ requires C, 36·1; H, 3·8%).

Quinol (5·5 g.) in pyridine (8 c.c.) with methanesulphonyl chloride (5·7 g.; 1 mol.), as described for the corresponding isopentane compounds, gave *p*-hydroxyphenyl methanesulphonate (1·5 g.; 15·9%), m. p. 73° not depressed by the com-

pound prepared by the former route, and quinol bismethanesulphonate (1·1 g.; 8·3%), m. p. 168°, also identical with the compound prepared as above.

2 : 5-*Dimethoxyphenylmethylsulphone.*—This *compound*, prepared as described for the *iso*amylsulphone, crystallised from alcohol in colourless prisms, m. p. 77°, depressed to 64° by admixture with *p*-anisyl methanesulphonate (Found : C, 49·6; H, 5·7. $C_9H_{12}O_4S$ requires C, 50·0; H, 5·6%).

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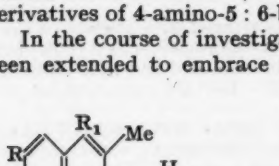
6. *Novel Types of Styrylquinolinium Compounds.*

By VLADIMIR A. PETROW.

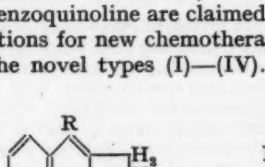
A new method has been developed for the synthesis of compounds related to 2-*p*-dimethylaminostyrylquinoline methochloride. Products derived from 3-methylquinoline, dihydro-β-quinindene, tetrahydroacridine, and phenanthridine have been prepared for examination as bactericides and trypanocides.

THE early observations of Browning, Cohen, Ellingworth, and Gulbransen (*Proc. Roy. Soc.*, 1924, *B*, **96**, 317) on the bactericidal action of the cyanine dyes led these workers to undertake a systematic study of the related styrylquinolinium compounds. These were found to possess strong antiseptic activity *in vitro* towards both *Staphylococcus aureus* and *B. coli*, not appreciably decreased by the presence of serum (*ibid.*, 1926, *B*, **100**, 293). Although attempts to increase their antiseptic power by the introduction of a further basic group at C_6 in the quinoline nucleus were not successful, yet these diamino-bases were shown in 1929 to constitute a new type of trypanocidal agent (*ibid.*, *B*, **105**, 99). The 4 : 4′-diamino-analogues were investigated by Ashley, Browning, Cohen, and Gulbransen (*ibid.*, 1933, *B*, **113**, 293) but were found to be less effective therapeutically. Styryl derivatives of 4-amino-5 : 6-benzoquinoline are claimed as bactericidal in G.P. 440,008.

In the course of investigations for new chemotherapeutic agents the observations of Browning *et al.* have been extended to embrace the novel types (I)—(IV). Condensation of *p*-dimethylaminobenzaldehyde and



(I.)



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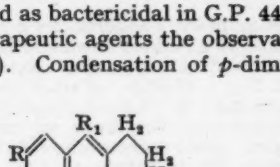

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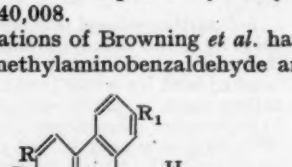

(IV.)

p-nitrobenzaldehyde with 1 : 2 : 3 : 4-tetrahydroacridine and 1 : 2 : 3 : 4-tetrahydro-6 : 7-benzacridine readily took place in the presence of anhydrous zinc chloride (cf. Borsche, *Annalen*, 1910, **377**, 110), but these *benzylidene* derivatives could not be converted into the methosulphates owing probably to steric hindrance. For instance, when 1-p-*dimethylaminobenzylidene*-1 : 2 : 3 : 4-*tetrahydroacridine* was boiled with methyl sulphate in nitrobenzene solution, the mixture immediately became intensely purple, yet the product which separated was a yellow water-soluble substance which regenerated the benzylidene compound on treatment with ammonia. Similar loose molecular complexes have been described by Browning, Cohen, Couper, and Gulbransen (*Proc. Roy. Soc.*, 1931, *B*, **109**, 51). When Kœnig's method (*J. pr. Chem.*, 1912, **86**, 172) was used and the corresponding methiodides heated with *p*-dimethylaminobenzaldehyde in aqueous-alcoholic solution in the presence of piperidine, moderate yields of (I) and (II) were obtained, the procedure failing for (III) and (IV). The use of higher alcohols as solvents and even fusion of the components at temperatures up to 200° failed to give compounds of the latter two types. It was ultimately found that the desired condensations could be achieved and compounds of all four types obtained in excellent yields by adding intimate equimolecular mixtures of the requisite methiodides with *p*-dimethylaminobenzaldehyde to boiling acetic anhydride. Separation of the styryl and the benzylidene compounds from the hot solution in an essentially pure condition usually occurred after 4—10 minutes' vigorous refluxing.

2 : 3-Dimethylquinoline methiodide readily condensed with *p*-dimethylaminobenzaldehyde to give 2-p-*dimethylaminostyryl*-3-*methylquinoline methiodide* (I; R = R_1 = H). Condensation of isatin with methyl ethyl ketone in aqueous ammonia gave 2 : 3-*dimethylquinoline*-4-*carboxyamide* (cf. G.P. 290,703), converted smoothly into 4-*amino*-2 : 3-*dimethylquinoline* by hypobromite oxidation. Both 4-*amino*-2 : 3-*dimethylquinoline methiodide* and its *acetyl* derivative failed to condense with *p*-dimethylaminobenzaldehyde to give (I; R = H, R_1 = NH_2 or NHAc) under a wide variety of conditions. The lesser reactivity of the related 4-aminoquinaldine methiodide, compared with quinaldine methiodide, had previously been noted by Browning *et al.* (1933, *loc. cit.*), who used fusion in the presence of piperidine for the analogous condensation. Reaction of 5-nitroisatin with methyl ethyl ketone in the presence of aqueous ammonia gave 6-*nitro*-2 : 3-*dimethylquinoline*-4-*carboxyamide*. Attempts to hydrolyse the amide to the acid, from which 6-amino-2 : 3-dimethylquinoline might be obtained for conversion into (I; R = NH_2, R_1 = H), were not successful. Reduction of the nitro-amide gave the corresponding 6-*amino*-2 : 3-*dimethylquinoline*-4-*carboxyamide*, which on dry distillation

with or without soda-lime, led surprisingly to *4-cyano-6-amino-2 : 3-dimethylquinoline* in high yield in place of the expected 6-amino-2 : 3-dimethylquinoline.

3-p-Dimethylaminobenzylidenedihydro-β-quinindene methiodide (II; R = H) was obtained in good yield from dihydro-β-quinindene methiodide. Attempts to prepare (II; R = NH_2) from *9-aminodihydro-β-quinindene methiodide* or its *acetyl* derivative were unsuccessful, no evidence of reaction being observed. Condensation of 5-nitroisatin with *cyclo*pentanone in the presence of ammonia gave a low yield of a product which could not be identified.

1-p-Dimethylaminobenzylidene-1 : 2 : 3 : 4-tetrahydroacridine methiodide (III; R = R_1 = H) and its 7-substituted derivatives were obtained from the methiodides of the corresponding tetrahydroacridines prepared by the method of Petrow (J., 1942, 693). *5-Amino-1 : 2 : 3 : 4-tetrahydroacridine methiodide* failed to condense with *p*-dimethylaminobenzaldehyde. The *acetyl* derivative gave evidence of reaction but a product could not be isolated.

The *9-p-dimethylaminostyrylphenanthridinium methiodides* (IV) were prepared from the corresponding 9-methylphenanthridine methiodides. *2-Nitro-4-methyldiphenyl* was prepared from the corresponding nitrotoluidine by the Gomberg reaction as improved by Elks, Haworth, and Hey (J., 1940, 1285), the derived *2-acetamido-4-methyldiphenyl* readily undergoing ring closure with phosphorus oxychloride to give *2 : 9-dimethylphenanthridine*. Difficulty was experienced in preparing *7-amino-9-methylphenanthridine*. Cyclisation of 4′-nitro-2-acetamidodiphenyl gave 7-nitro-9-methylphenanthridine in only 4% yield (cf. Morgan and Walls, J., 1932, 2227) for reasons discussed by these authors in a later publication (J., 1938, 390). It was ultimately found that the deactivating influence of the 4′-nitro-group could be circumvented by reduction to *4′-amino-2-acetamidodiphenyl*, followed by protection of the amino-group by benzoylation. The resulting *4′-benzamido-2-acetamidodiphenyl*, cyclised by phosphorus oxychloride to *7-benzamido-9-methylphenanthridine* in 62% yield, was smoothly hydrolysed to *7-amino-9-methylphenanthridine* * by syrupy phosphoric acid.

During the preparation of compounds of types (II) and (III) it was observed that the purity of the product was related to the time of heating of the components in acetic anhydride. Numerous experiments were required before optimum conditions were elaborated and analytically pure products obtained. The nature of the secondary change taking place was fully investigated only in the case of tetrahydroacridine methiodide. When an equimolecular mixture of tetrahydroacridine methiodide and *p*-dimethylaminobenzaldehyde was added to boiling acetic anhydride, rapid solution occurred. Separation of bright red crystals of the *benzylidene* compound took place after 4 minutes and was complete after 6 minutes. When the time of heating was prolonged to 1½ hours, a new *product* was obtained, separating in brilliant dark green needles and giving consistent analytical results corresponding to $C_{22}H_{23}N_2I$ (loss of methylene) or $C_{22}H_{21}N_2I$ (loss of methane). Incontrovertible evidence that the formation of this substance involved the loss of the methyl group attached to the ring nitrogen was furnished by the production of the identical product from *tetrahydroacridine ethiodide*. Its formulation as *1-p-dimethylaminobenzylidene-1 : 2 : 3 : 4-tetrahydroacridine hydriodide* followed from the observation that the corresponding *chloride* passed quantitatively on warming with a large volume of water into *1-p-dimethylaminobenzylidene-1 : 2 : 3 : 4-tetrahydroacridine*, identical in every respect with the material obtained by direct combination, and reconverted into the hydriodide identical with the dark green product above. As the ultraviolet absorption spectra of the green and the red iodide were nearly identical, it may be inferred that they are similarly constituted. The alternative formulation, a structure analogous to the pale yellow methiodide $C_9H_6{\cdot}CH{:}CH{\cdot}C_6H_4{\cdot}NMe_2I$, obtained by Rupe, Hagenbach, and Collin (*Helv. Chim. Acta*, 1935, **18**, 1400) by condensation of quinaldine with *p*-dimethylaminobenzaldehyde methiodide, cannot account for the intense colour—due to a resonance effect—of the green hydriodide and for the observed similarity of the absorption spectra, and can thus be ruled out.

The mechanism of the reaction between quinaldine alkiodides and *p*-dimethylaminobenzaldehyde in the presence of piperidine has been studied by Mills and Raper (J., 1925, **127**, 2466), who proved that the styryl compounds were formed through the intermediate formation of methylene bases which condensed with the *p*-dimethylaminobenzaldehyde to give compounds of the " allene " type, from which the styryl derivatives were obtained by addition of halogen hydride. Whilst this mechanism cannot be excluded in the formation of (I) and (IV) in acetic anhydride solution, an alternative mechanism must a priori be postulated to occur in the formation of (II) and (III). It is tentatively suggested that the condensations described in the present communication proceed through the intermediate formation of alkine-bases, which, as shown by Benrath (*J. pr. Chem.*, 1906, **73**, 387), can undergo dehydration under these experimental conditions.

The ultra-violet absorption curves of (II) and (III) over the range 2000—6000 A., kindly examined by Glaxo Laboratories Ltd., resemble closely that of *2-p-dimethylaminostyrylquinoline methiodide*, a substance with photosensitising properties. Both dihydro-β-quinindene methiodide and tetrahydroacridine methiodide also form highly coloured products with *p*-nitrosodimethylaniline. The preparation of cyanine dye analogues from bases containing active homocyclic methylene groups has not hitherto been described in the literature, and compounds (II) and (III) furnish the first examples of this type.

The pharmacology of the above compounds, as methochlorides, will be reported in detail elsewhere.

* (*Added in proof.*) Since the above was submitted for publication the author has learnt that Dr. L. P. Walls has prepared 7-amino-9-methylphenanthridine by a somewhat different method, the results being incorporated in Provisional British Patent Application No. 52/1944.

Experimental.

Melting points are corrected.

Benzylidene Derivatives of Tetrahydroacridine.—These were prepared by heating equimolecular amounts of the reactants in the presence of a little anhydrous zinc chloride at 120—130° for 2—3 hours. 1-p-*Nitrobenzylidene*-1 : 2 : 3 : 4-*tetrahydroacridine* formed orange octahedra from acetone–methyl alcohol, m. p. 145—146° (Found : C, 76·2; H, 5·4; N, 8·6. $C_{20}H_{16}O_2N_2$ requires C, 76·0; H, 5·1; N, 8·9%). 1-p-*Nitrobenzylidene*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*benzacridine* formed golden-yellow octahedra from benzene, m. p. 220—221° (Found : C, 78·6; H, 5·0; N, 7·1. $C_{24}H_{18}O_2N_2$ requires C, 78·7; H, 4·9; N, 7·7%). 1-p-*Dimethylaminobenzylidene*-1 : 2 : 3 : 4-*tetrahydroacridine* formed pale yellow, prismatic plates from aqueous acetone, m. p. 133—134° (Found : C, 84·0; H, 7·0; N, 9·1. $C_{22}H_{22}N_2$ requires C, 84·1; H, 7·0; N, 8·9%). 1-p-*Dimethylaminobenzylidene*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*benzacridine* formed golden-yellow needles from acetone, m. p. 211·5° (Found : C, 86·1; H, 6·6; N, 8·0. $C_{26}H_{24}N_2$ requires C, 85·7; H, 6·6; N, 7·7%). Methosulphates could not be obtained from these compounds (see p. 18).

Styryl Compounds.—The general method of preparation was as follows : An intimate, very finely powdered mixture of 0·1 g.-mol. of the methiodide and 0·12 g.-mol. of *p*-dimethylaminobenzaldehyde was added in one portion to boiling acetic anhydride [1000 ml. for (I), (II), and (III), and 1500 ml. for (IV)], and vigorous refluxing continued for 5—6 minutes [(I), (II), and (III)] or 10 minutes (IV). After cooling to room temperature, the product, which usually separated in the pure state, was collected and crystallised from a large volume of spirit where necessary. Yields are given in parentheses. The methochlorides were prepared by heating the finely powdered methiodides in methyl-alcoholic suspension with freshly precipitated silver chloride for 1—3 hours, and were crystallised from methyl alcohol or ether–methyl alcohol. 2-*p*-Dimethylaminostyrylquinoline methiodide had m. p. 269—270° (decomp.) (Found : I, 30·5. Calc. for $C_{20}H_{21}N_2I$: I, 30·5%). Rupe, Hagenbach, and Collin (*loc. cit.*) give m. p. 254° (decomp.).

2-p-*Dimethylaminostyryl*-3-*methylquinoline methiodide* (I; R = R_1 = H). (*a*) 2 : 3-Dimethylquinoline methiodide (2 g.) (Rohde, *Ber.*, 1889, **22**, 271) in absolute alcohol (75 ml.) was treated with *p*-dimethylaminobenzaldehyde (1 g.) and piperidine (1 ml.) for 1½ hours under reflux. The *product* formed small purplish needles from spirit, m. p. 255—255·5° (decomp.) (Found : C, 58·6; H, 5·4; N, 6·5; I, 29·5. $C_{21}H_{23}N_2I$ requires C, 58·6; H, 5·4; N, 6·5; I, 29·5%). Yield, 70%. (*b*) The *product* (93%) obtained by the acetic anhydride method was identical with the material obtained above (Found : C, 58·7; H, 5·4; N, 6·5; I, 29·5%). The *methochloride* formed dark purple needles, m. p. 245° (decomp.) (Found : Cl, 11·0. $C_{21}H_{23}N_2Cl$ requires Cl, 10·5%).

2 : 3-*Dimethylquinoline*-4-*carboxyamide.*—This *compound*, acicular plates from aqueous alcohol, m. p. 287—288° (Found : N, 14·3. $C_{12}H_{12}ON_2$ requires N, 14·0%), was prepared by heating isatin (12 g.), methyl ethyl ketone (18 ml.), and aqueous ammonia (80 ml., *d* 0·880) in a pressure bottle for 8 hours at 100°. The product (m. p. *ca.* 235°, yield 15 g.) was used direct.

4-*Amino*-2 : 3-*dimethylquinoline.*—The corresponding crude finely powdered amide (17·5 g.) was added in one portion with mechanical stirring to an ice-cold solution of bromine (15 g.) in 10% potassium hydroxide solution (250 ml.). After 45 minutes a further quantity of the potassium hydroxide solution (150 ml.) was added to the clear solution. After 5 minutes the mixture was heated at 100° for 30 minutes and boiled for 2—3 minutes. After standing overnight at 0°, the crude amine was collected. Yield, 15 g. 4-*Amino*-2 : 3-*dimethylquinoline*, purified *via* the hydrochloride, formed silky needles from aqueous acetone, m. p. 188·5—189·5° (Found : C, 76·3; H, 7·1; N, 16·4. $C_{11}H_{12}N_2$ requires C, 76·8; H, 7·0; N, 16·2%). The *methiodide* formed white needles from water, m. p. >310° (Found : I, 40·6. $C_{12}H_{15}N_2I$ requires I, 40·5%), stable to sodium bicarbonate. 4-*Acetamido*-2 : 3-*dimethylquinoline*, octahedra from aqueous methyl alcohol, m. p. 216—217° (Found : C, 72·9; H, 6·6; N, 13·2. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·5; N, 13·1%), was prepared by heating the base (4 g.), redistilled acetic anhydride (4 ml.), and dry pyridine (8 ml.) for 30 minutes. The *methiodide* formed octahedra or silky needles from water, m. p. 295—296° (decomp.) (Found : I, 35·8. $C_{14}H_{17}ON_2I$ requires I, 35·7%).

6-*Nitro*-2 : 3-*dimethylquinoline*-4-*carboxyamide*, prepared from 5-nitroisatin as above, separated from alcohol in pale yellow needles, m. p. 278—280° (Found : C, 58·5; H, 4·7; N, 17·0. $C_{12}H_{11}O_3N_3$ requires C, 58·8; H, 4·5; N, 17·1%).

6-*Amino*-2 : 3-*dimethylquinoline*-4-*carboxyamide*, pale yellow needles from water, m. p. 293·5—294·5° (decomp.) (Found : C, 67·0; H, 6·1; N, 19·5. $C_{12}H_{13}ON_3$ requires C, 67·0; H, 6·1; N, 19·5%), was prepared by reducing the crude nitro-amide (5 g.) in water (7 ml.) and spirit (18 ml.) to which a few drops of hydrochloric acid had been added, with reduced iron (7·5 g.) for 1½ hours on the water-bath.

4-*Cyano*-6-*amino*-2 : 3-*dimethylquinoline*, separating from aqueous acetone in pale yellow needles, m. p. 218·5—219·5° (Found : C, 73·1; H, 6·1; N, 21·1. $C_{12}H_{11}N_3$ requires C, 73·1; H, 5·6; N, 21·3%), was obtained (60—70% yield) by dry distillation of the amino-amide at atmospheric pressure. The *acetyl* derivative formed silky yellow needles from aqueous acetone, m. p. 238—239° (Found : C, 70·1; H, 5·6; N, 17·9. $C_{14}H_{13}ON_3$ requires C, 70·3; H, 5·4; N, 17·6%).

3-p-*Dimethylaminobenzylidenedihydro-β-quinindene Methiodide* (II; R = H).—(*a*) Dihydro-β-quinindene methiodide (6·0 g.), m. p. 212—213° (Borsche, *Annalen*, 1910, **377**, 121 gives m. p. 207°), *p*-dimethylaminobenzaldehyde (3 g.), absolute alcohol (80 ml.), and piperidine (2 ml.) were heated under reflux for 1 hour. The *product* formed brilliant blue needles, m. p. 235—236° (decomp.) (Found : N, 5·9; I, 28·3. $C_{22}H_{23}N_2I$ requires N, 6·3; I, 28·7%). Yield, 68%. (*b*) The product (95%), m. p. 238·5° (decomp.), obtained by the acetic anhydride method, was identical with the material obtained above (Found : C, 59·7; H, 5·4; N, 6·5; I, 28·9. $C_{22}H_{23}N_2I$ requires C, 59·7; H, 5·2; N, 6·3; I, 28·7%). The *methochloride* formed brilliant dark blue needles, m. p. 232° (decomp.) (Found : Cl, 10·0. $C_{22}H_{23}N_2Cl$ requires Cl, 10·1%).

9-*Aminodihydro-β-quinindene methiodide* formed needles from water, m. p. >320° (Found : I, 38·9. $C_{13}H_{15}N_2I$ requires I, 39·0%), stable to sodium bicarbonate. The *acetyl* derivative formed cubic crystals from water, m. p. 294—295° (decomp.) (Found : I, 34·6. $C_{15}H_{17}ON_2I$ requires I, 34·5%).

Condensation of Nitroisatin with cyclo*Pentanone.*—*cyclo*Pentanone (8 ml.) was added to nitroisatin (12 g.) dissolved in aqueous ammonia (80 ml., *d* 0·880), and the mixture heated for 8 hours at 100°. The black tarry mass was collected and extracted with a large volume of boiling spirit (charcoal), which on concentration deposited yellow plates (3·5 g.), m. p. 310—311° (decomp.), from alcohol (Found : C, 69·5, 69·5; H, 5·9, 5·8; N, 19·7, 19·8%).

1 : 2 : 3 : 4-*Tetrahydroacridine Derivatives.*—1-p-*Dimethylaminobenzylidene*-1 : 2 : 3 : 4-*tetrahydroacridine methiodide* (III, R = R_1 = H) (84%) formed brilliant scarlet needles, m. p. 236·5—237·5° (decomp.) (Found : C, 60·4; H, 5·5; N, 6·1; I, 28·0. $C_{23}H_{25}N_2I$ requires C, 60·5; H, 5·5; N, 6·1; I, 27·9%). The *methochloride* formed squat red rods, m. p. 230·5—231·5° (decomp.) (Found : Cl, 10·0. $C_{23}H_{25}N_2Cl$ requires Cl, 9·7%). 7-*Methyltetrahydroacridine methiodide* crystallised in pale yellow needles from water, m. p. 240—241° (decomp.) (Found : I, 37·5. $C_{15}H_{18}NI$ requires I, 37·5%). 1-p-*Dimethylaminobenzylidene*-7-*methyltetrahydroacridine methiodide* (III; R = CH_3, R_1 = H) (81%), formed red octahedra with a brilliant red reflex, m. p. 231·5—232·5° (decomp.) (Found : C, 61·3; H, 5·8; N, 6·1; I, 27·0. $C_{24}H_{27}N_2I$ requires C, 61·3; H, 5·7; N, 6·0; I, 27·0%). The *methochloride* separated in dark red octahedra with a green reflex, m. p. 219—220° (decomp.) (Found : Cl, 9·2. $C_{24}H_{27}N_2Cl$ requires Cl, 9·4%). 7-*Methoxytetrahydroacridine methiodide* formed yellow needles, from water, m. p. 247—248° (decomp.) (Found : I, 35·7. $C_{15}H_{18}ONI$ requires I, 35·8%). 1-p-*Dimethylaminobenzylidene*-7-*methoxytetrahydroacridine methiodide* (III; R = OMe, R_1 = H) (45%)

(600 ml. of acetic anhydride used) formed brilliant red needles with a golden reflex, m. p. 220—221° (decomp.) (Found : C, 58·9; H, 5·6; N, 5·8; I, 26·9. $C_{24}H_{27}ON_2I$ requires C, 59·3; H, 5·6; N, 5·8; I, 26·2%). The *methochloride* formed dark red octahedra, m. p. 208—209° (decomp.) (Found : Cl, 8·5. $C_{24}H_{27}ON_2Cl$ requires Cl, 9·0%). *7-Chlorotetrahydroacridine methiodide* formed pale yellow needles, m. p. 268—269° (decomp.) (Found : N, 4·0. $C_{14}H_{16}NCII$ requires N, 3·9%). *7-Chloro-1-p-dimethylaminobenzylidenetetrahydroacridine methiodide* (III; R = Cl, R_1 = H) (95%) crystallised in brilliant dark green plates, m. p. 229—230° (decomp.) (Found : C, 56·3; H, 4·8; N, 5·8. $C_{23}H_{24}N_2ClI$ requires C, 56·3; H, 4·9; N, 5·7%), and the *methochloride* in squat red needles, m. p. 215·5—216·5° (decomp.) (Found : Cl, 18·1. $C_{23}H_{24}N_2Cl_2$ requires Cl, 17·8%). *7-Azo-1 : 2 : 3 : 4-tetrahydroacridine*, obtained in 5% yield during the reduction of 7-nitrotetrahydroacridine, formed orange micro-crystals from nitrobenzene, m. p. 280—281° (decomp.) (Found : C, 79·6; H, 6·0; N, 14·1. $C_{26}H_{24}N_4$ requires C, 79·6; H, 6·1; N, 14·3%). *7-Acetamidotetrahydroacridine methiodide* formed pale yellow needles from water, m. p. 268—269° (decomp.) (Found : I, 33·3. $C_{16}H_{19}ON_2I$ requires I, 33·3%). *1-p-Dimethylaminobenzylidene-7-acetamidotetrahydroacridine methiodide* (III; R = NHAc, R_1 = H) was obtained in 30—50% yield by adding the methiodide (above) (8 g.) and *p*-dimethylaminobenzaldehyde to boiling acetic anhydride (400 ml.) to which a few drops of piperidine had been added. After 10 minutes' very vigorous refluxing the solution was filtered, and on cooling deposited the *benzylidene* derivative in brilliant red needles with a green reflex, m. p. 241·5—242·5° (decomp.) (Found : C, 58·1; H, 5·8; N, 8·1; I, 24·3. $C_{25}H_{28}ON_2I$ requires C, 58·5; H, 5·5; N, 8·2; I, 24·8%). The *methochloride* formed intense purple octahedra with a golden reflex, m. p. 202—203° (decomp.) (Found : Cl, 8·8. $C_{25}H_{28}ON_2Cl$ requires Cl, 8·4%). *5-Aminotetrahydroacridine methiodide* separated from water in faintly yellow needles, m. p. 300—301° (decomp.) (Found : I, 36·8. $C_{14}H_{17}N_2I$ requires I, 37·3%), stable to sodium bicarbonate. The *acetyl* derivative formed pale yellow octahedra from water, m. p. 240—241° (decomp.) (Found : I, 33·8. $C_{16}H_{19}ON_2I$ requires I, 33·3%). *1-p-Dimethylaminobenzylidenetetrahydroacridine hydriodide*, brilliant dark green needles, m. p. 263—264° (decomp.) (Found : C, 59·8; H, 5·0; N, 6·6; I, 28·7. $C_{23}H_{23}N_2HI$ requires C, 59·7; H, 5·2; N, 6·3; I, 28·7%), was obtained by adding tetrahydroacridine methiodide (33 g.) and *p*-dimethylaminobenzaldehyde (18 g.) to acetic anhydride (1500 ml.) and heating under reflux for 1½ hours. Yield, 13·5 g. The hydriodide was also obtained under identical conditions from *tetrahydroacridine ethiodide*, yellow needles from absolute alcohol, m. p. 224—225° (decomp.) (Found : I, 37·4. $C_{15}H_{19}NI$ requires I, 37·5%). The *hydrochloride*, nearly black octahedra from ether–methyl alcohol, m. p. 232—233° (decomp.) (Found : Cl, 10·0. $C_{23}H_{23}N_2HCl$ requires Cl, 10·0%), passed on heating with 70 vols. of water under reflux into *1-p-dimethylaminobenzylidenetetrahydroacridine*, m. p. 133—134° (Found : C, 84·1; H, 6·8; N, 9·6. $C_{23}H_{22}N_2$ requires C, 84·1; H, 7·0; N, 8·9%), identical with the material described above obtained by direct interaction. After addition of a few drops of hydriodic acid (*d* 1·7) to the solution of the benzylidene derivative in boiling acetic anhydride, the characteristic dark green needles of the hydriodide separated on cooling, identical with the compound described above.

Phenanthridine Derivatives.—9-p-*Dimethylaminostyrylphenanthridine methiodide* (IV; R = R_1 = R_2 = H) (74%), dark red needles with a green reflex, m. p. 236·5—237·5° (decomp.) (Found : C, 61·8; H, 4·9; N, 6·1; I, 27·2. $C_{24}H_{23}N_2I$ requires C, 61·8; H, 4·9; N, 6·0; I, 27·3%), was prepared from 9-methylphenanthridine methiodide, m. p. 270—271° (decomp.) (Found : I, 37·9. Calc. for $C_{14}H_{15}NI$: I, 37·9%) (Pictet and Hubert give 246—247°, *Ber.*, 1896, **29**, 1185). The *methochloride* formed dark purple needles with a green reflex, m. p. 239—240° (decomp.) (Found : Cl, 9·5. $C_{24}H_{23}N_2Cl$ requires Cl, 9·5%). 5-Nitro-2-*p*-toluenesulphonamidodiphenyl was prepared by the method of G.P. 163,516. For hydrolysis the nitro-derivative (5 g.) was added to a mixture of concentrated sulphuric acid (10 ml.) and glacial acetic acid (10 ml.), warmed until solution was complete, and poured into ice-water (200 ml.) (cf. Bell, J., 1928, 2773). Reduction of 3-nitro-9-methylphenanthridine by the method of Morgan and Walls (1932, *loc. cit.*) gave a high-melting yellow product, so the following procedure was adopted : Finely powdered 3-nitro-9-methylphenanthridine (10 g.), suspended in concentrated hydrochloric acid (50 ml.), was treated with stannous chloride (27·5 g.) in concentrated hydrochloric acid (30 ml.), reaction being completed by heating for 30 minutes on the water-bath. After 12 hours at 0° the product was collected, the regenerated base refluxed with acetic anhydride (50 ml.) for 20 minutes, diluted to 250 ml., and the filtered solution made alkaline with ammonia. The acetyl derivative was crystallised once from spirit. Yield, 6·6 g. 3-Acetamido-9-methylphenanthridine methiodide formed very pale yellow needles from water, m. p. 268·5—269·5° (decomp.) (Found : I, 32·6. Calc. for $C_{17}H_{17}ON_2I$: I, 32·4%) (no m. p. is given by Morgan and Walls, J., 1938, 394).

3-*Acetamido*-9-p-*dimethylaminostyrylphenanthridine methiodide* (IV; R = NHAc, R_1 = R_2 = H) (80%) formed dark crimson-brown needles, m. p. 267·5—268·5° (decomp.) (Found : C, 59·5; H, 5·1; N, 8·1; I, 24·4. $C_{26}H_{26}ON_3I$ requires C, 59·4; H, 5·3; N, 8·0; I, 24·2%). The *methochloride*, intense mauve needles with a brassy reflex, m. p. 264·5—265·5° (decomp.) (Found : Cl, 8·0. $C_{26}H_{26}ON_3Cl$ requires Cl, 8·2%), was hydrolysed by heating the compound (8 g.) with concentrated hydrochloric acid (40 ml.) and water (40 ml.) for 1 hour under reflux, evaporating the solution to dryness on the water-bath, and crystallising the residue from absolute alcohol, the *amino-methochloride hydrochloride* being obtained in small brown needles (Found : Cl, 16·7. $C_{24}H_{25}N_3Cl_2$ requires Cl, 16·7%).

Reduction of 4′-nitro-2-acetamidodiphenyl (10 g.) (Bell, J., 1927, 95), suspended in spirit (40 ml.) and water (10 ml.), with reduced iron (15 g.) and a trace of hydrochloric acid for 1½ hours on the water-bath gave *4′-amino-2-acetamidodiphenyl*, cubes from alcohol–light petroleum, m. p. 118·5—119·5° (Found : C, 74·3; H, 6·3; N, 12·4. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%). *4′-p-Toluenesulphonamido-2-acetamidodiphenyl* formed octahedra from aqueous methyl alcohol, m. p. 201—202° (Found : S, 8·4. $C_{21}H_{20}O_3N_2S$ requires S, 8·4%). Attempts at ring closure with phosphorus oxychloride did not give satisfactory results. *4′-Benzamido-2-acetamidodiphenyl*, dazzling white plates from spirit, m. p. 216—217° (Found : C, 76·4; H, 5·4; N, 8·6. $C_{21}H_{18}O_2N_2$ requires C, 76·4; H, 5·5; N, 8·5%), was cyclised to *7-benzamido-9-methylphenanthridine*, pale yellow needles from methyl alcohol, m. p. 214—215° (Found : C, 77·8; H, 5·4; N, 8·3. $C_{21}H_{16}ON_2,CH_3{\cdot}OH$ requires C, 76·7; H, 5·8; N, 8·1%. The material dried in a vacuum at 135° gave C, 81·2; H, 5·2; N, 9·1. $C_{21}H_{16}ON_2$ requires C, 80·8; H, 5·1; N, 9·0%). The *picrate* formed a felted mass of pale yellow micro-needles from spirit, m. p. 277° (decomp.) (Found : N, 13·0. $C_{21}H_{16}ON_2,C_6H_3O_7N_3$ requires N, 12·9%). *7-Amino-9-methylphenanthridine*, needles from spirit, m. p. 232·5—233·5° (Found : C, 80·4; H, 6·1; N, 13·8. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8; N, 13·5%), was prepared by hydrolysis of the benzamido-derivative with 2 parts of syrupy phosphoric acid for 1½ hours at 200—210°. *7-Acetamido-9-methylphenanthridine*, obtained as a felted mass of faintly yellow needles from aqueous alcohol, m. p. 248—249° (Found : C, 76·8; H, 5·8; N, 11·3. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%), formed a *methiodide*, orange silky needles from water, m. p. 278—279° (Found : I, 32·0. $C_{17}H_{17}ON_2I$ requires I, 32·4%). 7-*Acetamido*-9-p-*dimethylaminostyrylphenanthridine methiodide* (IV; R = R_2 = H, R_1 = NHAc) (80%) formed small dark green needles, m. p. 270—271° (decomp.) (Found : C, 59·2; H, 5·3; N, 7·8; I, 24·6. $C_{26}H_{26}ON_3I$ requires C, 59·4; H, 5·3; N, 8·0; I, 24·2%). The *methochloride* crystallised in brilliant dark green needles, m. p. 276—277° (decomp.) (Found : Cl, 7·8. $C_{26}H_{26}ON_3Cl$ requires Cl, 8·2%). The *amino-methochloride hydrochloride* formed a brown microcrystalline powder from ether–alcohol (Found : Cl, 16·6. $C_{24}H_{25}N_3Cl_2$ requires Cl, 16·7%). *2-Nitro-4-methyldiphenyl* was prepared in 51% yield from *m*-nitro-*p*-toluidine by the method of Elks, Haworth, and Hey (*loc. cit.*) and formed a pale yellow oil with a faint odour of bitter almonds, b. p. 208°/11 mm. (Found : C, 73·0; H, 5·2; N, 7·0. $C_{13}H_{11}O_2N$ requires C, 73·2; H, 5·2; N, 6·6%). *2-Amino-4-methyldiphenyl*, obtained from the

nitro-compound in 83% yield by reduction with reduced iron in aqueous alcohol, b. p. 183°/11 mm. (Found : C, 85·4; H, 7·3; N, 8·0. $C_{13}H_{13}N$ requires C, 85·2; H, 7·1; N, 7·7%), formed an *acetyl* derivative, plates from aqueous methyl alcohol, m. p. 150·5—151·5° (Found : C, 79·7; H, 6·6; N, 6·5. $C_{15}H_{15}ON$ requires C, 80·0; H, 6·7; N, 6·2%), cyclised by phosphorus oxychloride to 2 : 9-*dimethylphenanthridine*, octahedra from light petroleum, m. p. 104·5—105·5°, b. p. 240°/14 mm. (Found : C, 87·0; H, 6·4; N, 6·9. $C_{15}H_{13}N$ requires C, 87·0; H, 6·3; N, 6·8%). Yield, 73%. 2 : 9-*Dimethylphenanthridine methiodide* formed yellow micro-needles from water, m. p. 261—262° (decomp.) (Found : I, 36·6. $C_{16}H_{16}NI$ requires I, 36·4%). 9-p-*Dimethylaminostyryl*-2-*methylphenanthridine methiodide* (IV; R = R_1 = H, R_2 = CH_3) (83%) formed small purplish needles with a greenish-brown reflex, m. p. 246—247° (decomp.) (Found : C, 62·2; H, 5·4; N, 6·1; I, 26·9. $C_{25}H_{25}N_2I$ requires C, 62·5; H, 5·2; N, 5·8; I, 26·5%). The *methochloride* formed permanganate-like crystals, m. p. 240—240·5° (decomp.) (Found : Cl, 8·7. $C_{25}H_{25}N_2Cl$ requires Cl, 9·1%).

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7. *The Configuration of Naturally Occurring Mixed Glycerides. Part I. The Configuration of Oleodistearin from Various Natural Sources.*

By M. L. MEARA.

The melting and transition points of oleodistearin, isolated from six seed fats of which it is a prominent constituent, have been determined. They are identical in each instance with those of β-oleodistearin and different from those of the unsymmetrical α-oleodistearin (the corresponding constants for the synthesised α- and β-oleodistearins have recently been determined by Daubert, Fricke, and Longenecker, *J. Amer. Chem. Soc.*, 1943, **65**, 2142, 2144; 1944, **66**, 289, 690).

THE component glycerides of a large number of animal and vegetable fats have now been determined, for the most part by Hilditch and his co-workers, but there has been little definitive work to determine the positional configuration of these glycerides, mainly owing to the difficulty in isolating individual glycerides in a sufficient state of purity, and until comparatively recently the properties of synthetic mixed glycerides, needful for reference purposes, were not sufficiently characterised. The properties of the saturated symmetrical and unsymmetrical mixed glycerides have now been described by Malkin and his collaborators (J., 1939, 103, 577, 1141, 1518), and the corresponding unsaturated glycerides are now being synthesised and studied by Daubert, Longenecker, *et al.* (*loc. cit.*). From the available data it is therefore now possible to specify the configuration of a number of individual naturally occurring glycerides provided they be isolated in a state of sufficient purity.

The configuration of oleodistearin, which was amongst the first of the natural mixed glycerides to be isolated, forms the subject of the first paper of this series.

The reported m. p.'s of the majority of specimens of oleodistearin isolated from natural products lie between 42° and 44°, some authors reporting a transition point at 28—30°. An early synthesis of β-oleodistearin (Kreis and Hafner, *Ber.*, 1903, **36**, 276) by heating αα′-distearin with oleic acid under reduced pressure gave a low yield of oleodistearin, melting after crystallisation at 42°, and after fusion at 28—30°. A specimen isolated from cacao butter melted in similar circumstances at 44—45° and 27—28°, and from this these authors concluded that the substance isolated was the unsymmetrical isomer. Later knowledge of the component glycerides of cacao butter indicates that their material consisted of the symmetrical isomer contaminated with small amounts of fully saturated glycerides. Grün (*Ber.*, 1907, **40**, 1778) from oleic anhydride and αα′-distearin obtained a product which melted at 42°; after one year, however, it melted at 41° and 55°, and when cooled and reheated, at 42°. Amberger and Bromig (*Biochem. Z.*, 1922, **130**, 257) prepared α-oleodistearin of m. p. 42°, but were unable to prepare the symmetrical isomer. Hilditch and Saletore (*J. Soc. Chem. Ind.*, 1933, **52**, 101T), from the reaction between oleyl chloride and αα′-distearin, obtained a product which on oxidation gave what appeared to be a mixture of azelao-glycerides as judged from the m. p.'s of the fractions obtained by crystallisation, the main fraction melting at 62·5—63·5°. Oxidation of oleodistearin from *Allanblackia Stuhlmannii* gave a product of this m. p. which remained unchanged on admixture with some of the main fraction of synthetic material. Both symmetrical and unsymmetrical oleodistearin have now been synthesised by methods which have proved trustworthy in the synthesis of saturated mixed triglycerides of known composition, oxalyl chloride being used in the preparation of oleyl chloride, thus eliminating the use of thionyl chloride which gives oleyl chloride in low yields and doubtful purity (Daubert and Longenecker, *loc. cit.*).

The saturated–unsaturated mixed triglycerides resemble the saturated mixed triglycerides in exhibiting the same type of polymorphism as that described by Malkin and his collaborators (*loc. cit.*) for the saturated mixed triglycerides. Each glyceride is capable of existing in four forms, a vitreous form IV, two intermediate forms III and II, and the stable crystalline form I (in the American nomenclature), these forms corresponding to Malkin's vitreous, α-, β′-, and β-forms, respectively. The transition points of the three metastable forms and the m. p. of the stable forms are well defined and can be determined with comparative ease.

Experimental.

Oleodistearin has been isolated in quantity from the following seed fats by fractional crystallisation from acetone: *Allanblackia Stuhlmannii* (Hilditch and Saletore, *loc. cit.*), *Allanblackia floribunda* and *Allanblackia parviflora* (Meara and Zaky, *J. Soc. Chem. Ind.*, 1940, **59**, 25), *Palaquium oblongifolium* (Hilditch and Stainsby, *ibid.*, 1934, **53**, 197T), *Garcinia Indica* (Hilditch and Murti, *ibid.*, 1941, **55**, 16), and *Pentadesma butyracea* (Hilditch and Saletore, *ibid.*, 1931, **50**, 468T).

The oleodistearin from the above fats was recrystallised several times from pure redistilled B.G.S. acetone (15—25 ml. per g.), the flasks being well lagged with cotton wool and suspended in a room, the temperature of which was maintained as constant as possible. The deposited crystals were filtered off and dried in an desiccator for several days.

The m. p. of the stable crystalline form was obtained in a capillary tube in the normal way. The form III transition point was obtained by allowing the molten mass to solidify and redetermining the m. p. On keeping the specimen at this temperature for a short time, it solidified, and on raising the temperature of the bath it remelted at form II transition point. If this operation was carried out too slowly, the m. p. of the stable form was obtained, since form II had been converted into form I. The transition point of form II was checked by immersing the capillary tube with the specimen in form III into a beaker of water, the temperature of which was adjusted so that the specimen just melted, prolonged immersion causing it to change over again to form I. The transition point of form IV was obtained by immersing the capillary tube containing the molten specimen first in a freezing mixture and then in a beaker of water, the temperature being adjusted and the process repeated until the substance gave rise to a definite change in appearance, due either to expansion and filling up of the cracks caused by cooling or to melting followed by rapid re-solidification.

Transition and melting points of different specimens of oleodistearin.

	IV.	III.	II.	I.
From *Allanblackia floribunda*	23 —23·5°	29·5°	37·0°	43·3—43·6°
,, ,, *parviflora*	23 —24	29 —30	36·0	43·0—43·3
,, ,, *Stuhlmannii*	23 —24	29 —30	37·5	43·0—43·3
,, *Garcinia Indica*	23·5—24·5	29 —29·5	37·5	43·3—43·5
,, *Pentadesma butyracea*	23·5—24	29·3—29·6	37·0	43·5—43·8
,, *Palaquium oblongifolium*	22 —23	29 —29·5	37·5	43·0—43·5
Synthetic β-oleodistearin *	22·3	29·8	37—37·6	41·6
,, α- ,, *	?	?	?	38·5

* Daubert *et al.* (*locc. cit.*).

Discussion.—It is seen from the above data that the transition and melting points of all the specimens of oleodistearin examined lie very near to those given for synthetic β-oleodistearin, and that of form I differs markedly from that recorded for α-oleodistearin. This, taken in conjunction with the evidence available from oxidation of synthetic and naturally occurring β-oleodistearin, makes it conclusive that the oleodistearins so far examined occurring in the above seed fats consist entirely of symmetrical β-oleodistearin.

Little can yet be said in regard to the seeming paradox that, concurrently with a very pronounced tendency to elaborate glycerides of as mixed a character (*i.e.*, containing as many different acyl groups) as possible, the oleodistearin in this group of fats is restricted to one configurational form only. It may be pointed out, however, that the proportion of oleic acid in all the fats under consideration (cf. table below) is of a similar order, and that it is less than that of the saturated acids (of which stearic is the main component). Whether this feature is of any significance in determining the position taken by the oleic group in oleodistearin remains to be seen.

Component acids of the fats studied (weight %).

Seed fat.	Myristic.	Palmitic.	Stearic.	Oleic.	Linoleic.
Allanblackia floribunda	0·2	3·2	56·8	39·4	0·4
,, *parviflora*	—	3·5	52·7	43·8	—
,, *Stuhlmannii*	—	3·1	52·6	44·1	0·2
Garcinia Indica	—	2·5	56·4	39·4	1·7
Pentadesma butyracea	—	5·4	46·1	48·5	—
Palaquium oblongifolium	0·2	5·9	54·0	39·9	—

It is not practicable to define the configuration of the stearodiolein which accompanies oleodistearin in these fats until further refinements now under investigation can be added to the technique of separation of the lower-melting glycerides in a sufficient state of purity for thermal investigation.

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8. *The Configuration of Naturally Occurring Mixed Glycerides. Part II. The Configuration of Some Monopalmito-glycerides from Various Natural Sources.*

By M. L. Meara.

The melting and transition points of palmitodistearin, produced by hydrogenation of glycerides originally present as palmito-oleostearins, palmitodioleins or palmito-oleolinoleins in cacao butter, cottonseed oil and pig back fat, and separated by fractional crystallisation, have been determined. In all cases the thermal data obtained coincided with those of β-palmitodistearin and were different from those of α-palmitodistearin (as determined by Malkin and his collaborators, J., 1939, 103, 577).

In continuation of the study of the configuration of naturally occurring glycerides, monopalmito-glycerides derived from cacao butter, cottonseed oil, and pig back fats have now been investigated.

Monopalmito-glycerides from Cacao Butter.—Hilditch and Stainsby (*J. Soc. Chem. Ind.*, 1936, **55**, 95T) determined the component glycerides of cacao butter by determining first the component acids of the fat, followed by a determination of the nature and amounts of fully saturated glycerides obtained on hydrogenating the fat to intermediate stages of saturation. A second method was then evolved, *viz.*, partial separation of the fat into its component glycerides by crystallisation from acetone, each fraction then being examined in a manner identical with the first method. From these investigations the authors were able to state that the specimen of cacao butter examined contained the following: oleopalmitostearin 52%, oleodistearin 19%, stearodiolein 12%, palmitodiolein 9%, oleodipalmitin 6%, and palmitodistearin 2%. Much of the trebly mixed glyceride was believed to be β-palmito-oleostearin, whereas oleo-disaturated glycerides were believed to have occurred mainly as the symmetrical isomers.

A selected fraction *A* (see below), rich in palmito-stearins, had been obtained from the fractional crystallisation of the fully saturated glycerides produced on hydrogenation of the cacao butter to an iodine value of 6·6, together with fractions *B*, *C*, *D*, m. p. 67·5°, 66·5°, 65·0°, sap. equiv. 288·5, 287·9, 287·8 (Calc. for palmitodistearin: 287·3). These fractions had been reserved and were the materials used in the present investigation.

Monopalmito-glycerides from Cottonseed Oil.—Hilditch and Maddison (*J. Soc. Chem. Ind.*, 1940, **59**, 162), applying the technique of low-temperature crystallisation from acetone solution to a specimen of cottonseed oil, thereby separated it into six fractions of different solubility and iodine value. One of these fractions with the following component acids (% wt.): myristic 2·6, palmitic 25·8, stearic 2·0, arachidic 1·1, tetradecenoic 0·1, hexadecenoic 1·1, oleic 24·9, linoleic 42·4, was found to consist almost wholly of mono-saturated di-unsaturated glycerides, for the most part palmito-oleolinolein and palmitodilinolein. Hydrogenation of a portion of this fraction, followed by crystallisation to remove myristo- and oleo-glycerides, gave the material used as the source of palmitostearin in this investigation.

Monopalmito-glycerides of Pig Back Fat.—In an investigation of the body fats of the pig, Hilditch and Stainsby (*Biochem. J.*, 1935, **29**, 94) prepared a series of fats progressively hydrogenated to iodine values of 35·8, 18·7, and 10·0. The non-fully-saturated portions of these fats were removed by oxidation, and the composition of the fully saturated residue determined. In each case this was found to consist principally of palmitodistearin, together with much smaller quantities of stearodipalmitin; crystallisation from ether gave yields of material of the order of 80% of the total palmitodistearin present, which was considered by Hilditch and Stainsby to be pure β-palmitodistearin and was therefore reserved for more complete investigation.

Experimental.

Specimens of palmitodistearin concentrates from the above sources were further crystallised from pure ether (40 ml. per g.) in the manner described in Part I (preceding paper). The same technique for the determination of transition and melting points was employed, it being found necessary, however, to keep a specimen at a particular transition point much longer, in the case of the saturated mixed triglycerides than in that of the unsaturated glycerides (Part I, *loc. cit.*), for it to become transformed into the next more stable modification. The values for transition and melting points of palmitodistearin from these sources are compared with those recorded for synthetic β- and α-palmitodistearin (Malkin and Meara, J., 1939, 103; Carter and Malkin, *ibid.*, p. 577) in the following table.

Melting and transition points of palmitodistearin from various sources.

	IV.	III.	II.	I.
Palmitodistearin from cacao butter (*A*)	50°	56°	64°	68°
,, ,, ,, ,, (*B*)	49—50	55	64	67·5
,, ,, ,, ,, (*C*)	48·5—49·5	55	63	66·5
,, ,, ,, ,, (*D*)	49	55	64	67·0
,, ,, cottonseed oil	50	56	64	67·7
,, ,, pig back fat (*A*)	49	55	64·5	67·5
,, ,, ,, ,, (*B*)	50	55—56	64	67·5
,, ,, ,, ,, (*C*)	49	55	63—66	67
Synthetic β-palmitodistearin	50	56	64	68
,, α- ,, ...	50	57	61	65

Discussion.—These values, obtained from hydrogenated naturally occurring glycerides, accord remarkably well with those recorded for the synthetic symmetrical (β) palmitodistearin. In view of the relative ease with which compounds of m. p. 67—68° have been obtained, and of the well-known difficulty attending the separation of mixtures of isomeric palmitostearins by crystallisation, these observations point definitely to the virtually exclusive occurrence of β-palmito-oleostearin and β-palmitodiolein in cacao butter, β-palmito-oleolinolein and β-palmitodilinolein in cottonseed oil, and β-palmito-oleostearin and β-palmitodiolein in pig back fat.

These results suggest that in all three fats (in which palmitic forms 20—30% of the total fatty acids) the palmitic group occupies the β- or symmetrical position in the mixed triglycerides, whether these are palmito-oleostearin or palmito-diunsaturated glycerides. It is hoped to extend these studies to include a more detailed investigation of the palmito-glycerides in a series of structurally related animal (pig, ox, and sheep) depot fats, and in some vegetable fats, *e.g.*, palm oils, in which palmitic acid is present in quantity.

The author wishes to thank Professor T. P. Hilditch for his advice and criticism during the investigation described in Parts I and II.

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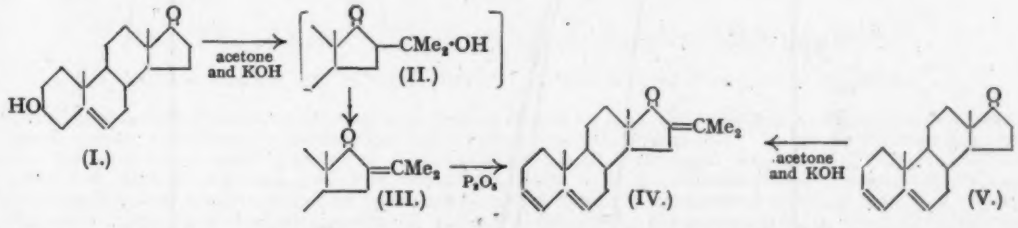
9. 16-iso*Propylideneandrostene Derivatives.*

By Walter C. J. Ross.

An improved method for the preparation of 16-*iso*propylidene-Δ^5-androsten-3-ol-17-one (III) is described. Dehydration of (III) affords 16-iso*propylidene*-$\Delta^{3:5}$-*androstadien*-17-*one* (IV), which on reduction by the Kishner–Wolff procedure yields 16-iso*propylidene*-$\Delta^{3:5}$-*androstadiene*.

trans-Dehydroandrosterone (I) condenses with acetone in the presence of sodium and dry ether to give the *iso*propylidene compound (III), though in poor yield; the higher homologue of (III), from *trans*-dehydroandrosterone and methyl ethyl ketone, is more easily obtained, but here also the yield is only 30% (Butenandt, Schmidt-Thomé, and Weiss, *Ber.*, 1939, **72**, 417).



During the hydrolysis of some *trans*-dehydroandrosterone acetate residues, it was observed that a sparingly soluble, crystalline product was formed; this was resolved by chromatographic adsorption into a less adsorbed fraction (A) and a more adsorbable, resinous fraction (B). The latter was acetylated, the acetate of (III), m. p. 186—189°, being obtained. The unknown *benzoate*, m. p. 210—212°, was also easily prepared; both these esters on hydrolysis gave the parent keto-alcohol, m. p. 223° (Butenandt *et al.*, *loc. cit.*). The formation of these compounds was traced to the presence of acetone in the methyl alcohol used as a solvent in the hydrolysis, thus suggesting that the condensation of acetone with *trans*-dehydroandrosterone should proceed easily under the right conditions. This was confirmed by heating pure *trans*-dehydroandrosterone acetate with acetone in the presence of methyl-alcoholic potassium hydroxide, whereby an 80% yield of the *iso*propylidene compound (III) was obtained. On one occasion an unstable substance, m. p. 180° with evolution of gas, was formed, but when this was filtered off and warmed with methanol it was readily converted into (III). The intermediate compound is probably the keto-diol (II); owing to its instability, it was not possible to prepare a specimen for analysis.

The less adsorbable compound (A) has the composition $C_{22}H_{30}O$ and is evidently produced from (III) by the loss of the elements of water; it could, in fact, be obtained from (III) by heating in benzene with phosphoric oxide. It is therefore 16-iso*propylidene*-$\Delta^{3:5}$-*androstadien*-17-*one* (IV). Similar dehydration of *trans*-dehydroandrosterone (I) yielded $\Delta^{3:5}$-androstadien-17-one (V) (compare Burrows, Cook, Roe, and Warren, *Biochem. J.*, 1937, **31**, 950), and this condenses with acetone in the presence of methyl-alcoholic potassium hydroxide to give an excellent yield of the *iso*propylidene compound (IV).

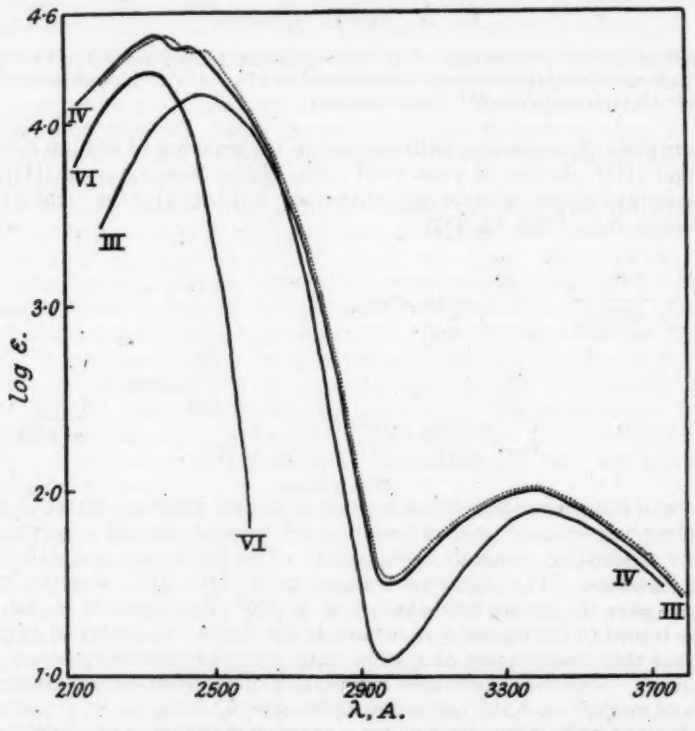
The carbonyl group in the *iso*propylidene compounds is in a relatively protected position, for no semicarbazones could be prepared by the usual methods. Nevertheless, 16-*iso*propylidene-$\Delta^{3:5}$-androstadienone (IV) can be reduced by the Kishner–Wolff procedure to give 16-iso*propylidene*-$\Delta^{3:5}$-*androstadiene*, m. p. 140—144°. An attempted reduction of 16-*iso*propylidene-Δ^5-androsten-3-ol-17-one (III) gave an unidentified *product*, m. p. 190—192°, apparently having the composition $C_{29}H_{34}O_3$.

Confirmation of the structures assigned to compounds (III) and (IV) and to 16-*iso*propylidene-$\Delta^{3:5}$-androstadiene is afforded by the examination of their ultra-violet absorption spectra (Figure); (III) shows selective absorption of light with a primary maximum at 2500 A., log $\varepsilon_{max.} = 4{\cdot}17$, and a secondary maximum at 3380 A., log $\varepsilon_{max.} = 2{\cdot}0$. This type of absorption is characteristic of $\alpha\beta$-unsaturated carbonyl compounds (Evans and Gillam, J., 1941, 815). The absorption curve for the diene shows a maximum at 2350 A., log $\varepsilon_{max.} = 4{\cdot}28$, similar to that for $\Delta^{3:5}$-androstadien-17-one (log $\varepsilon_{max.} = 4{\cdot}26$ at 2345 A.) and $\Delta^{3:5}$-cholestadiene (log $\varepsilon_{max.} = 4{\cdot}30$ at 2350 A.) (Burrows *et al.*, *loc. cit.*). The summation of the absorption curves for (III) and the diene is shown in the figure by the dotted line: the resemblance of this to the curve for (IV) is good evidence for the presence of both chromophores in the last compound.

The *iso*propylidene compounds form needles or prisms according to the conditions of crystallisation. They clearly exist in two forms, for if the temperature is raised quickly the m. p. is lower than when it is raised slowly. This is almost certainly due to the transformation of the low-melting into the high-melting variety at the point of fusion of the former. This behaviour has also been observed in the pregnene series of compounds, particularly with Δ^5-pregnenolone, $\Delta^{5:16}$-pregnadienolone, and progesterone. The last, as prepared in our laboratories, melts at 121° in a rapidly heated but at 128° in a slowly heated bath. If the specimen is first fused at 121° and allowed to resolidify, it will then invariably melt at 128°. A similar behaviour has been observed in the case of Δ^4-cholestenone (Jones and Barton, J., 1943, 602).

The ease of condensation with acetone is a characteristic of the 16-methylene group and is not shared by

the 2-methylene group in Δ^4-cholestenone, since the latter is unchanged on treatment with acetone and methyl-alcoholic potassium hydroxide.



III, 16-*iso*Propylidene-Δ^5-androsten-3-ol-17-one. IV, 16-*iso*Propylidene-$\Delta^{3:5}$-androstadien-17-one. VI, 16-*iso*Propylidene-$\Delta^{3:5}$-androstadiene.

Experimental.

(All m. p.'s, which are uncorrected, were taken in a slowly heated bath.)

Hydrolysis of trans-*Dehydroandrosterone Acetate Residues.*—90 G. of resinous material (obtained by the oxidation of cholesteryl acetate dibromide) were refluxed for 2 hours with 90 g. of potassium hydroxide in 400 c.c. of commercial methyl alcohol. The solution, from which solid had begun to separate, was then allowed to cool overnight. The heavy crop of prismatic needles was filtered off and well washed with methyl alcohol, giving 13 g. of solid, m. p. 170—180°. A benzene solution of the product was percolated through a column of activated alumina. From this column benzene eluted 6 g. of solid (A), m. p. 193—195° after recrystallisation from alcohol (Found : C, 84·9; H, 9·8. $C_{22}H_{30}O$ requires C, 85·1; H, 9·8%). This *substance* (IV) formed long needles if the solution was cooled slowly, or prisms if the cooling was more rapid. The more strongly adsorbed material was removed from the column by washing with ether, and the resinous fraction (B) thus obtained was divided into two parts. One part was acetylated by refluxing with acetic anhydride for ½ hour, giving an *acetyl* derivative, m. p. 186—189°, after several recrystallisations from acetone–methyl alcohol (Found : C, 77·4; H, 9·5. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·3%). The other part, on treatment with benzoyl chloride in pyridine, yielded the *benzoate*, m. p. 210—212°, which formed flattened needles from acetone (Found : C, 79·4; H, 8·9. $C_{27}H_{36}O_3$ requires C, 79·4; H, 8·9%).

16-iso*Propylidene*-Δ^5-*androsten*-3-*ol*-17-*one.*—2 G. of *trans*-dehydroandrosterone acetate were dissolved in a mixture of 10 c.c. each of acetone and methyl alcohol, and after the addition of 2 g. of potassium hydroxide the mixture was refluxed for 1 hour. The cooled mixture was diluted with water and extracted with ether. The residue obtained by evaporating the dried extract formed felted needles from methyl alcohol, m. p. 223° (Found : C, 80·2; H, 10·0. $C_{22}H_{32}O_2$ requires C, 80·4; H, 9·8%). The yield of recrystallised material was 1·6 g. This *ketone* was also obtained by the hydrolysis of the acetate and the benzoate described above.

On one occasion, cooling of the condensation mixture yielded a product, m. p. 180° with evolution of gas, which readily dissolved in methyl alcohol, but when the solution was warmed the less soluble *iso*propylidene compound, m. p. 223°, was deposited.

Δ^4-Cholestenone was recovered unchanged when heated with acetone–methyl alcohol in the presence of potassium hydroxide as described above.

Dehydration of 16-iso*Propylidene*-Δ^5-*androsten*-3-*ol*-17-*one.*—500 Mg. of the *iso*propylidene compound in 5 c.c. of benzene were boiled for ½ hour with 1 g. of phosphoric oxide, which became purple. The benzene solution was percolated through a column of activated alumina and evaporated, and the residue crystallised twice from methyl alcohol, giving, on slow cooling, long needles of 16-*iso*propylidene-$\Delta^{3:5}$-androstadien-17-one, m. p. 192—194°, not depressed by admixture with substance (A) (Found : C, 84·7; H, 9·8%).

$\Delta^{3:5}$-*Androstadien*-17-*one.*—1 G. of *trans*-dehydroandrosterone was dehydrated as described above; the product formed plates, m. p. 85°, from aqueous methyl alcohol. The semicarbazone, formed by heating 200 mg. of the ketone under reflux with 200 mg. of semicarbazide acetate in 5 c.c. of methyl alcohol, melted at 290° (decomp.). $\Delta^{3:5}$-Androstadien-17-one condensed with acetone under the conditions described above to give compound (A), m. p. and mixed m. p. 192—194°. Compound (A) did not form a semicarbazone when refluxed with a solution of semicarbazide acetate.

Reduction of 16-iso*Propylidene*-$\Delta^{3:5}$-*androstadien*-17-*one.*—1 G. of ketone, 2·6 c.c. of 98% hydrazine hydrate, and

0·5 g. of sodium in 10 c.c. of alcohol were heated in a sealed tube for 16 hours at 210°. The product obtained by dilution with water and extraction with ether was not homogeneous; it was therefore dissolved in light petroleum (b. p. 40—60°) and percolated through a column of alumina. The percolate contained a solid, m. p. 139—143°, which was further purified by sublimation at 120°/0·001 mm. The 16-iso*propylidene*-$\Delta^{3:5}$-*androstadiene* now formed plates from methyl alcohol, m. p. 140—144° (Found: C, 88·5; H, 10·8. $C_{22}H_{32}$ requires C, 89·1; H, 10·9%).

Attempted Reduction of 16-iso*Propylidene*-Δ^5-*androsten*-3-*ol*-17-*one*.—The substance was treated with hydrazine hydrate and sodium ethoxide as described above. The *product* crystallised from ether–light petroleum (b. p. 60—80°) in magnificent flattened needles, m. p. 190—192° with evolution of gas (Found: C, 74·4; H, 10·9. $C_{20}H_{34}O_3$ requires C, 74·5; H, 10·6%).

The absorption spectra were measured by Mr. E. A. Braude. The author's thanks are due to Professor G. A. R. Kon for his interest in this work and to Organon Laboratories Ltd. for permission to publish the results.

RESEARCH DEPARTMENT, ORGANON LABORATORIES LTD., LONDON. [*Received, September 18th*, 1944.]

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10. *The Action of Sodium on o-Xylylene Dibromide.**

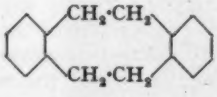
By WILSON BAKER, R. BANKS, DONALD R. LYON, and FREDERICK G. MANN.

Sodium reacts with *o*-xylylene dibromide in boiling dioxan to give a 6% yield of s-*dibenz*cyclo*octadiene* (I) and much smaller yields of di-*o*-tolylethane and s-*tribenz*cyclo*dodecatriene* (II). In boiling ether no apparent reaction occurs unless a small quantity of ethyl acetate is added, whereupon *o*-xylene (5%), di-*o*-tolylethane (6%), the dodecatriene (II), and a product which may be 3 : 4 : 7 : 8-*dibenzoxa*cyclo-$\Delta^{3:7}$-*nonadiene* (III) are formed, together with a high yield of an amorphous product having a composition identical with that of (III).

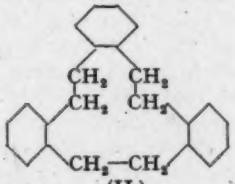
The stereochemistry of the hydrocarbons (I) and (II) is discussed; the structure of (I), which can theoretically exist in two isomeric forms, is established.

WHEN a solution of *o*-xylylene dibromide in dry dioxan was refluxed in the presence of an excess of "powdered" sodium, a slow but spontaneous reaction occurred, which was complete after 15—20 hours' boiling. From the product there have been isolated s-*dibenz*cyclo*octadiene* (I), m. p. 108·5°, in *ca.* 6% yield, and much smaller quantities of αβ-di-*o*-tolylethane, $C_6H_4Me{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_4Me$, m. p. 65°, and s-*tribenz*cyclo*dodecatriene* (II), m. p. 184·5°. The structures of (I) and (II) are discussed below.

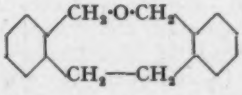
When, however, a solution of *o*-xylylene dibromide in ether was boiled with an excess of sodium, no apparent reaction occurred even after many hours' boiling. The addition of a small quantity of ethyl acetate induced a moderately rapid reaction, with the separation of much amorphous organic material. From the solution, however, there have been isolated *o*-xylene (*ca.* 5%), αβ-di-*o*-tolylethane (*ca.* 6%), and smaller quantities of



(I.)



(II.)



(III.)

the *cyclo*dodecatriene (II) and of a compound $C_{16}H_{16}O$, m. p. 97·5—98·5°, whose properties indicate that it is probably 3 : 4 : 7 : 8-*dibenzoxa*cyclo-$\Delta^{3:7}$-*nonadiene* (III). It is noteworthy that, although the yields of the ditolylethane and the hydrocarbon (II) were greater in the ether than in the dioxan experiments, the *cyclo*octadiene (I) was not isolated from the former reaction product, although there were indications of its presence in minute quantity.

The amorphous product which separated from the ether experiments was soluble in other organic liquids, but it has not been obtained crystalline. It is an extremely stable product, with the same empirical formula as the crystalline ether (III); molecular-weight determinations indicate a formula $(C_{16}H_{16}O)_{6-9}$, but owing to experimental difficulties, the number of $C_{16}H_{16}O$ units in the molecule is still uncertain (p. 29).

The formation of *o*-xylene and the ditolylethane in the ether experiments can be readily explained: the interaction of the sodium and the ethyl acetate would generate nascent hydrogen, which would in turn reduce small quantities of *o*-xylylene dibromide and also of the first product of the Wurtz condensation, *viz.*, αβ-di-*o*-ω-bromotolylethane, $C_6H_4(CH_2Br){\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_4{\cdot}CH_2Br$. *o*-Xylene was not detected in the dioxan experiments where no ethyl acetate was present, and the minute yield of ditolylethane in these experiments may have originated from traces of water unavoidably present. In the ether experiments, the presence of a trace of water in conjunction with the sodium could account for the formation of the cyclic ether (III) from the above dibromotolylethane.

The structure and stereochemistry of the two cyclic hydrocarbons (I) and (II) are of great interest.

The identification of the former as s-dibenz*cyclo*octadiene (I) rests on the following evidence. (*a*) Although

* The experiments in dioxan were carried out at Oxford in 1937—1938 (W. B. and R. B.) and those in ether at Cambridge (D. R. L. and F. G. M.). The two investigations were performed independently and for different purposes, but after the work was complete their closely similar nature became known, and it was decided to unite the results in this joint publication.

a Wurtz reaction to give (I) or similar compounds of higher molecular weight is the most probable condensation, it is not impossible that, by a Friedel–Crafts type of reaction in the presence of a reducing agent, a compound such as 2 : 3-dimethyl-9 : 10-dihydroanthracene might be formed. The hydrocarbon (I) has, however, considerable stability towards oxidising agents, whereas 2 : 3-*dimethyl*-9 : 10-*dihydroanthracene* is very readily oxidised. This property of ready oxidation would also apply to other similar isomerides of even more improbable occurrence. (*b*) Dr. Edna M. Davidson, of Bedford College (University of London), working in the Cavendish Laboratory of the University of Cambridge, has investigated the hydrocarbon (I) crystallographically. She finds that the molecule has a centre of symmetry. (*c*) Dr. G. B. B. McI. Sutherland has subjected both the hydrocarbons $C_{16}H_{16}$ (I) and $C_{24}H_{24}$ (II) to infra-red spectroscopic examination, and finds that neither possesses a methyl group. This cumulative evidence proves that the hydrocarbon of formula $C_{16}H_{16}$ must have the structure (I).

It should be noted, however, that *s*-dibenz*cyclo*octadiene (I) is probably capable of existing in two stereoisomeric forms. If models are constructed in which the correct intervalency angles are fixed, but in which the methylene carbon atoms can (when the structure permits) twist about their valency bonds, the possible existence of two distinct forms (Figs. 1 and 1A) * becomes apparent. In the first form (Fig. 1), the molecule is rigid, and possesses a plane and a centre of symmetry. In the second form (Fig. 1A) the central ring system is mobile, and a gentle twisting pressure, applied, for instance, to the right-hand benzene ring, causes the latter to fold over until it reaches the extreme position above the former left-hand ring (Fig. 1B). If this pressure is now reversed, the upper ring twists back until the former position (Fig. 1A) is attained, and may then continue twisting until it occupies the same relative position below the left-hand ring as it formerly occupied above, *i.e.*, its structure is now again identical with that shown in Fig. 1B. It is important to note that, whereas the structure acquired at each extreme of this twisting process (Fig. 1B) has two planes of symmetry, neither this nor any intermediate structure (such as Fig. 1A) has a centre of symmetry. It follows that the hydrocarbon isolated must be the form (Fig. 1) having the rigid configuration. A search for the second form of the hydrocarbon (I) in the original reaction product has so far proved unsuccessful. Höhn (Richter–Anschütz, " Chemie der Kohlenstoff-Verbindungen," 1935, II, 2, 392) has suggested for the two known forms of disalicylide " chair " and " trough " structures, presumably similar in type to those shown in Fig. 1 and Fig. 1A : in the disalicylides, however, the central ring contains two oxygen atoms.

A model of *s*-tribenz*cyclo*dodecatriene (II), similarly constructed, shows that the central ring system possesses considerable mobility, and a large number of strainless phases is possible : four of these are shown in Figs. 2A—2D. There is one form (Fig. 2A) in which the molecule is planar, but the three central methylene groups are almost certainly too near together for this form to exist. Gentle manipulation of the ring system, however, readily converts this form into that shown in Fig. 2B, in which the top and the right-hand $CH_2{\cdot}C_6H_4{\cdot}CH_2$ units are parallel, the plane of the latter unit being below that of the top unit; the left-hand unit is necessarily obliquely inclined to these planes, having its top CH_2 group in the plane of the right-hand unit and its right-hand CH_2 group in the plane of the top unit. This form (Fig. 2B) is therefore strictly asymmetric. Further rotational pressure converts this form into that shown in Fig. 2C, in which the plane of the paper is a plane of symmetry. The left-hand $CH_2{\cdot}C_6H_4{\cdot}CH_2$ unit in this form can be readily folded downwards below the other two units to give the fourth form (Fig. 2D), in the photograph of which, however, the model has been realigned to show its character more clearly. It will be seen that this form possesses three planes of symmetry and also, running vertically through the centre of the molecule, a direct 3-fold axis of symmetry.

It must be emphasised that the model allows ready interconversion of all these forms without rupture of the central ring, or change of the valency angles or interatomic distances. The compound (II) is therefore of particular interest and it is hoped later to determine by *X*-ray analysis the particular form adopted by the molecule in the crystalline state. The minute size of the crystals makes such an analysis difficult. Preliminary optical examination, kindly undertaken by Dr. M. Perutz, shows that the crystals are either orthorhombic or monoclinic. It is very unlikely, therefore, that the molecules can have trigonal symmetry, and consequently the forms shown in Fig. 2A and Fig. 2D are of improbable occurrence in the crystalline state.

Experimental.

The *o*-xylylene dibromide was prepared by Perkin's method (J., 1888, **53**, 5) and recrystallised until pure.

Condensation of o-*Xylylene Dibromide with Sodium.*—(A) *In dioxan.* The dibromide (20 g., 1 mol.), dissolved in pure dioxan (175 c.c., previously refluxed and distilled over sodium), was added to sodium (6·5 g., 3·7 atoms, previously " powdered " under toluene), and the mixture heated on the water-bath (15—20 hours) until the supernatant liquid ceased to give the Beilstein halogen test. Alcohol was first added to the cold mixture to remove unchanged sodium, and then water. The sticky, cream-coloured precipitate was extracted with warm benzene, the extract dried, and the solvent removed by distillation. The residue was worked up by either (*a*) steam-distillation or (*b*) extraction with alcohol.

(*a*) Steam-distillation yielded a colourless solid (0·4—0·6 g., *ca.* 6%), m. p. 105—107°, which after several crystallisations from alcohol furnished *s-dibenz*cyclo*octadiene* (I), hexagonal plates, m. p. 108·5° (Found : C, 92·4, 92·1; H, 7·9, 7·8; *M*, by Rast's method in 10% camphor solution, 212, 222. $C_{16}H_{16}$ requires C, 92·3; H, 7·7%; *M*, 208). Concentration of the mother-liquor from the first recrystallisation yielded a very small amount of αβ-di-*o*-tolylethane, m. p. 56—58°, which when mixed with an authentic sample, prepared by the method of Moritz and Wolffenstein (*Ber.*, 1899, **32**, 2531) or by that of Carré (*Compt. rend.*, 1909, **148**, 1109; *Bull. Soc. chim.*, 1909, **5**, 489), had m. p. 57—59°.

(*b*) The residue was refluxed for 12 hours with alcohol (500 c.c.), filtered hot, and concentrated (charcoal). The filtrate deposited a colourless solid mixture (this softened at *ca.* 100° and melted at 177—179°) which was distilled in

* In all the models shown in the photographs, the hydrogen atoms have been omitted for simplicity.

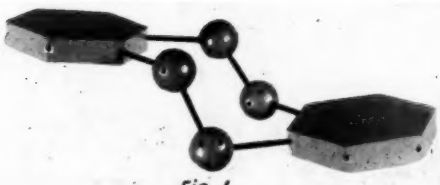


Fig. 1

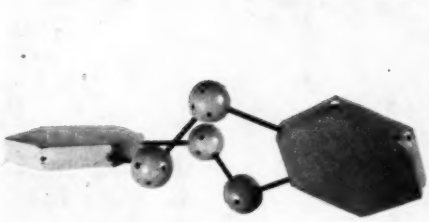


Fig. 1A

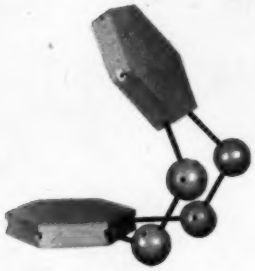


Fig. 1 B.

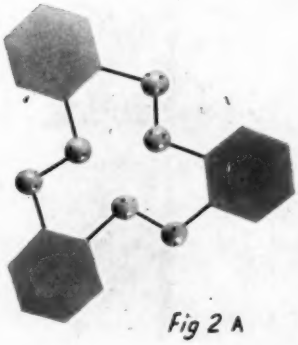


Fig 2 A

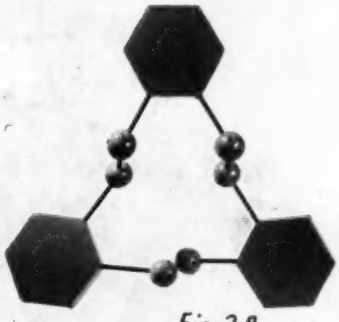


Fig. 2 B

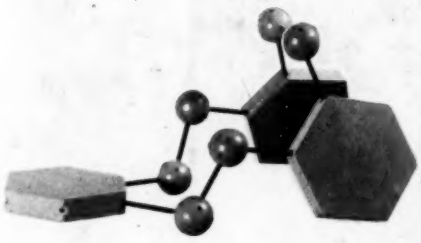


Fig. 2C

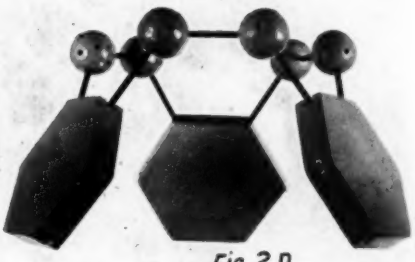


Fig 2 D

[To face p. 28.

steam. The distillate deposited the compound (I), m. p. 107—108°, identical with that isolated in (*a*) above. The non-volatile residue, when recrystallised from alcohol, gave impure *s-tribenzcyclododecatriene* (II), which softened at *ca.* 160° and melted at 177—179° [Found : C, 92·2; H, 7·9; *M* (Rast) 305, 322. $C_{24}H_{24}$ requires C, 92·3; H, 7·7%; *M*, 312]. The yield of (II) was small and complete purification could not be achieved; the higher yield obtained in ether (see below) enabled the pure hydrocarbon to be isolated.

s-Dibenz*cyclo*octadiene (I) is very stable towards oxidising agents; it is unaffected by a boiling acetone solution of potassium permanganate, and is scarcely attacked by a cold chromic acid–acetic acid mixture (cf. 2 : 3-dimethyl-9 : 10-dihydroanthracene below). It is not attacked under the usual Kuhn–Roth conditions for estimation of *C*-methyl groups (*Z. angew. Chem.*, 1931, **44**, 847; *Ber.*, 1933, **66**, 1274).

(B) *In ether.* Fine sodium wire (40 g.; 4·4 atoms) was added to a solution of the dibromide (105·6 g., 1 mol.) in dry ether (600 c.c.), and the mixture refluxed. Ethyl acetate (2 c.c.) was added to the boiling mixture, and the refluxing was then continued for 24 hours, further additions of ethyl acetate (each of 2 c.c.) being made at the end of the 5th, 15th, and 20th hour of heating; even after 5 hours' heating much of the sodium had disintegrated and a considerable amount of amorphous solid had separated, and this change appeared to be complete after the 24 hours' heating. The liquid was now filtered, and the cream-coloured amorphous residue washed on the filter with ether. The united filtrate and washings were distilled. After the ether had thus been removed, the liquid residue was separated into the following four fractions, the last three being selected arbitrarily, as no sharp separation at this stage appeared possible : (i) b. p 38—48°/15 mm., 2 g.; (ii) b. p. 100—140°/0·05 mm., 3 g.; (iii) b. p. 140—210°/0·05 mm., 4 g.; (iv) b. p. 210—260°/0·05 mm., 2 g.

Fraction (i), a clear mobile liquid, on refractionation gave *o*-xylene, b. p. 141—143° (Found : C, 90·25; H, 9·8. Calc. for C_8H_{10} : C, 90·5; H, 9·5%); 5%.

Fraction (ii) readily crystallised when set aside. On refractionation, the main bulk distilled at 110—120°/0·03 mm., and again solidified. Recrystallisation from alcohol furnished *αβ*-di-*o*-tolylethane, m. p. 65—66°, alone and when mixed with an authentic sample (Found : C, 91·6; H, 8·4; *M*, ebullioscopic in 1·47% benzene solution, 210; in 0·88% acetone solution, 201. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%; *M*, 210); 2·5 g., 6%.

Fraction (iii), a thick viscous oil, could not be obtained crystalline and was consequently redistilled, the following fractions being arbitrarily selected : (iii*a*) b. p. 140—143°/0·03 mm.; (iii*b*) b. p. 148—150°/0·01 mm.; (iii*c*) b. p. 150—175°/0·03 mm.; (iii*d*) b. p. 175—210°/0·03 mm. Fractions (iii*a*) and (iii*c*) were pale yellow, viscous liquids which did not crystallise even when set aside for many months, or when subjected to various treatments. Fraction (iii*b*), a thick viscous liquid, also remained liquid for many months. Ultimately, however, it was mixed with a small volume of alcohol and seeded with the *cyclo*octadiene (I), whereupon crystallisation rapidly occurred. The colourless crystals so obtained were bromine-free, and when twice recrystallised from alcohol furnished 3 : 4 : 7 : 8-*dibenzoxa*cyclo-$\Delta^{3:7}$-*nonadiene* (III), m. p. 97·5—98·5° (Found : C, 85·7; H, 7·2; *M*, ebullioscopic in 0·53% benzene solution, 225; in 1·13% solution, 225. $C_{16}H_{16}O$ requires C, 85·7; H, 7·2%; *M*, 224). A mixture of this compound with the *cyclo*octadiene (I) of m. p. 108·5° had m. p. 75—104°. The structure (III) assigned to this compound was suggested by the facts that (*a*) the compound was recovered unchanged after 30 minutes' boiling in acetic anhydride solution, and after 20 minutes' boiling in an acetic acid–phenylhydrazine mixture, (*b*) its alcoholic solution gave no coloration with ferric chloride. Fraction (iii*d*), a brown viscous liquid, slowly crystallised when set aside. Vigorous stirring with a small amount of alcohol and petrol gave a clear separation of colourless crystals, which when collected and recrystallised from alcohol, gave *s*-tribenz*cyclo*dodecatriene (II), m. p. 184·5° (Found : C, 92·3; H, 7·9%; *M*, ebullioscopic in 1·53% benzene solution, 321; in 1·00% acetone solution, 295).

Fraction (iv) also crystallised when set aside. When treated precisely as (iii*d*) above, it furnished a further crop of the *cyclo*dodecatriene (II), m. p. 184·5° (Found : C, 91·95; H, 7·8%).

The original condensation in ether was repeated, but the residue obtained after the evaporation of the ether from the united filtrate and washings was now distilled in steam. The following separated in turn from the distillate; (i) *o*-xylene; (ii) colourless crystals, m. p. 45—55°, 2·5 g.; (iii) a very small quantity of an oil which partly crystallised. Alcoholic recrystallisation of (ii) gave crystals, m. p. 57—59°, unaffected by two more recrystallisations, or by admixture with authentic *αβ*-di-*o*-tolylethane of m. p. 66·5°; concentration of the first mother-liquor gave a further small crop, m. p. 63—65°, similarly unaffected.

Fraction (iii) when triturated with alcohol gave colourless crystals, m. p. 57—59°, also unaffected by admixture with the ditolylethane. It is clear from these results that the crystalline product in the aqueous distillate must have been the ditolylethane containing a trace of some impurity, presumably the *cyclo*octadiene (I), which could not be removed by alcoholic crystallisation.

The cream-coloured amorphous powder which separated during the original condensation in ether clearly represented the main product of the reaction. After it had been washed with ether, and traces of unchanged sodium removed by hand, the powder was thoroughly extracted with cold water and dried : the residue (20 g.) was now bromine-free. This product had no definite m. p.; on being heated, it slowly became viscous above 50° and ultimately formed a mobile liquid. It was freely soluble in cold benzene, toluene, xylene, chloroform, and ethylene dibromide, and almost insoluble in cold alcohol, acetone, ethyl acetate, and ether. All attempts to crystallise this compound failed : contact with organic solvents in which it was not freely soluble usually gave either a sticky semi-solid mass or a viscous suspension. In an attempted purification, two samples, obtained in different preparations, were thoroughly washed with cold alcohol and then dried in a vacuum over phosphoric anhydride. A third sample was mixed with acetone and set aside for several days : it became sticky on immediate contact with the acetone but later resolidified, and was then collected, washed with alcohol, and dried as before. The three samples were analysed [Found : C, 85·4, 85·8, 85·7; H, 7·3, 7·4, 7·1; *M*, determined with the first sample ebullioscopically in 2·10% benzene solution, 1830; in 1·99% solution, 1870; in 2·91% solution, 1860; cryoscopically in 1·22% ethylene dibromide solution, 2010. $(C_{16}H_{16}O)_9$ requires C, 85·7; H, 7·2%; *M*, 1792. $(C_{16}H_{16}O)_9$ requires *M*, 2016]. The above data indicate that the product is probably homogeneous because the very small temperature differences involved in the molecular-weight determinations do not distinguish decisively between the above two alternative values.

This product was recovered apparently unchanged after it had been (*a*) precipitated from benzene solution by addition of alcohol, collected, and washed in turn with alcohol and acetone, (*b*) boiled with a mixture of constant b. p. hydriodic acid and acetic anhydride for 5 hours, (*c*) boiled for several hours with either dilute hydrochloric acid or 10% aqueous sodium hydroxide. When heated at 14 mm. pressure, it melted readily, but even on strong heating it furnished only a very small amount of a viscous distillate which could not be obtained crystalline.

The following hydrocarbons were prepared for direct comparison with (I) before the structure of the latter had been determined by other means.

2 : 3-*Dimethyl*-9 : 10-*dihydroanthracene*. 2 : 3-Dimethylanthracene (1 g.; Elbs and Eurich, *J. pr. Chem.*, 1890, **41**, 5; Fairbourne, J., 1921, **119**, 1573) was refluxed in alcohol (30 c.c.), and 2% sodium amalgam added occasionally in small portions until a test portion of the solution gave no orange coloration when added to a benzene solution of picric acid (12 hours); during this period, a few drops of acetic acid were added at hourly intervals. The solution was

then poured into water, and the precipitated 2 : 3-*dimethyl*-9 : 10-*dihydroanthracene* collected and recrystallised from alcohol; plates, m. p. 122° (Found: C, 92·4; H, 7·8. $C_{16}H_{16}$ requires C, 92·3; H, 7·7%). This compound, unlike (I), rapidly reduces a boiling acetone solution of potassium permanganate, and a cold chromic acid–acetic acid mixture.

2 : 3′ : 4′-*Trimethyldiphenylmethane*. Anhydrous aluminium chloride (10 g.) was slowly added to a mixture of *o*-xylene (20 g.) and *o*-toluoyl chloride, the latter having been prepared from *o*-toluic acid (10 g.) and thionyl chloride (25 c.c.). When the vigorous initial reaction had subsided, the mixture was heated on a water-bath for 6 hours, and then poured into water and extracted with ether. Distillation of the extract gave 2 : 3′ : 4′-*trimethylbenzophenone*, b. p. 192—197°/15 mm., which readily solidified (11 g.) and after draining and repeated crystallisation from petrol (b. p. 40—60°) was ultimately obtained as colourless crystals, m. p. 55—58° (Found: C, 85·1; H, 7·5. $C_{16}H_{16}O$ requires C, 85·7; H, 7·2%). A solution of this ketone (5 g.) in toluene (10 c.c.) was refluxed for 24 hours with amalgamated zinc (10 g.), concentrated hydrochloric acid (8 c.c.), and water (17·5 c.c.), a further addition of the acid (5 c.c.) being made every 6 hours. Extraction with ether, followed by distillation, gave 2 : 3′ : 4′-*trimethyldiphenylmethane* as a colourless oil (4 g.), b. p. 173°/21 mm. (Found: C, 91·4; H, 8·6. $C_{16}H_{18}$ requires C, 91·4; H, 8·6%). This compound was slowly oxidised by a boiling acetone solution of potassium permanganate and by a cold chromic acid–acetic acid mixture.

Dr. Davidson reports on the hydrocarbon (I) as follows:

"The specimen consisted of small colourless highly birefringent crystals, in the form of thick irregular tablets, having the sign of the birefringent positive and the dominant face of the tablet (100).

"The unit cell dimensions and the space-group were determined by single-crystal *X*-ray oscillation and Weissenberg photographs, and gave $a = 6{\cdot}80$ A., $b = 6{\cdot}84$ A., $c = 13{\cdot}63$ A., $\beta = 100°$; the space-group was monoclinic $P2_1/c$.

"The density determined by flotation in aqueous acetone was 0·986 g./c.c., giving the number of molecules in the unit cell as two. Since there are four general positions in the space group $P2_1/c$, it follows that the molecules cannot lie in general positions, but must lie in special positions, *i.e.*, they must lie on the centres of symmetry in the unit cell, and therefore the molecules themselves must possess centres of symmetry. On cooling in liquid air, the crystals showed no pyroelectric effect, which also indicates the absence of a polar structure."

Dr. M. Perutz reports on the hydrocarbon (II) as follows:

"The compound forms lath-shaped needles with straight extinction parallel to the needle axis and strong negative birefringence. There are only two faces parallel to the needle axis, and the angle between them is 87°; this angle excludes the trigonal and hexagonal systems and indicates that the crystals are either orthorhombic or monoclinic. In these circumstances it is unlikely that the molecule itself has trigonal symmetry, and therefore the forms shown in Fig. 2A and 2D are unlikely to occur in the crystalline state. The form shown in Fig. 2A is improbable for structural reasons (because of the close approach of the central methylene groups), while that shown in Fig. 2D would hardly give rise to needle-shaped crystals with such strong negative birefringence."

We gratefully acknowledge the help we have received from Dr. E. M. Davidson, Dr. G. B. B. McI. Sutherland, and Dr. M. Perutz. We are also greatly indebted to Mr. E. E. Webb of the Cambridge University Physical Chemical Department for photographic assistance.

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THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE.

[*Received, October 26th*, 1944.]

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11. *The Preparation and Properties of* 2-*Substituted* iso*Arsindolines. The Synthesis of* spiro-*Arsonium Salts.*

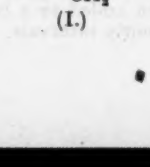
By DONALD R. LYON and FREDERICK G. MANN.

o-Xylylene dibromide in the presence of sodium and ether reacts with phenyl- and methyl-dichloroarsine to give 2-*phenyl*- and 2-*methyl*-iso*arsindoline* (I, R = Ph and R = Me). The latter combines with *o*-xylylene dibromide to give the quaternary *salt* (IV), which on heating undergoes cyclisation and loss of methyl bromide, furnishing As-spiro-*bis*iso*arsindolinium bromide* (V). *spiro*-Arsonium salts of this type have not previously been prepared.

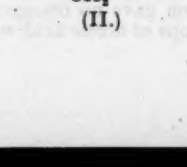
Arsenobenzene can be readily prepared by the action of sodium upon ethereal phenyldichloroarsine.

Preliminary tests indicate that 2-*phenyl*iso*arsindoline dihydroxide* may prove to be an effective drug against *Trypanosoma congolense* infection.

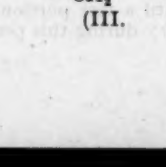
ALTHOUGH several types of organic compound containing an arsenic atom as part of a five-membered ring are known, the arsenic analogues of the *iso*indolines have not previously been described. We find that when an ethereal solution of equimolecular quantities of *o*-xylylene dibromide and phenyldichloroarsine is refluxed with metallic sodium in an atmosphere of nitrogen, no apparent reaction occurs; the addition of ethyl acetate, however, promotes the desired reaction, and, provided air be carefully excluded throughout, distillation of the final filtered solution ultimately furnishes 2-*phenyl*iso*arsindoline* (I, R = Ph) as a colourless liquid, b. p. 136—138°/0·3 mm., in 18% yield. Certain by-products are also formed. For instance, the arsine is initially contaminated with hydrocarbons formed by the direct action of the sodium on the dibromide (see preceding paper), and the undistilled residue contains arsenobenzene, formed by the direct action of the sodium on the dichloride. This novel method for preparing arsenobenzene is discussed later.



(I.)



(II.)

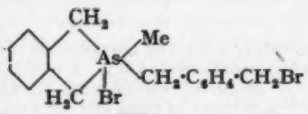


(III.)

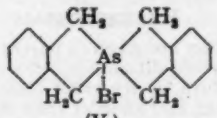
2-Phenyl*iso*arsindoline has the normal properties of a tertiary arsine. Oxidation with nitric acid readily gives the crystalline *hydroxy-nitrate* (II, X = NO_3), which in turn, treated with aqueous sodium hydroxide, furnishes the water-soluble *2-phenylisoarsindoline dihydroxide* (II, X = OH); the latter can be dehydrated to the *oxide* (III), which, however, on exposure to damp air rapidly absorbs water, re-forming the dihydroxide. The latter also reacts with other acids; *e.g.*, with hydrobromic acid it gives the crystalline *hydroxy-bromide* (II, X = Br) and with picric acid the *hydroxy-picrate* (II, X = $C_6H_2O_7N_3$). In view of the therapeutic importance of the dihydroxide, we have investigated in some detail its production by other means from the arsine (I, R = Ph). This arsine unites with bromine to give the white, crystalline arsine dibromide, which is decomposed by alkalis to form the dihydroxide. The arsine is also oxidised by chloramine-T (sodio-toluene-*p*-sulphonchloroamide), furnishing *2-phenylisoarsindoline hydroxy-toluene*-p-*sulphonamide* (II, X = $C_7H_7{\cdot}SO_2{\cdot}NH$), which is also readily decomposed by alkalis to furnish the dihydroxide. The arsine can also be directly converted into the dihydroxide by the action of hydrogen peroxide or aqueous potassium permanganate; the latter reagent apparently also gives other products and the yield of dihydroxide is low.

The arsine dihydroxide reacts with hydrogen sulphide to form the colourless *arsine sulphide* (as III). Methyl iodide unites directly with the arsine, giving the quaternary salt, *2-phenyl-2-methylisoarsindolinium iodide*.

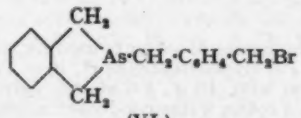
Initial attempts to prepare *2-methylisoarsindoline* (I, R = Me) by the action of sodium on a boiling ethereal solution of equimolecular quantities of *o*-xylylene dibromide and methyldichloroarsine in the presence of ethyl acetate were unsuccessful, although interesting by-products were isolated. When, however, an excess of the dichloroarsine (1·5 mols.) was used, with prolonged boiling, 2-methyl*iso*arsindoline, b. p. 115°/17 mm., was obtained, but only in 4% yield. This arsine gives arsonium salts more readily than its phenyl analogue; *e.g.*, it unites vigorously with methyl iodide to give 2 : 2-*dimethylisoarsindolinium iodide*. Furthermore, it also unites with *o*-xylylene dibromide to give 2-o-(*bromomethyl*)*benzyl*-*2-methylisoarsindolinium bromide* (IV). This salt when heated loses methyl bromide, giving the highly crystalline As-spiro-*bis*iso*arsindolinium bromide* (V), characterised also by conversion into the corresponding *iodide* and *picrate*. This synthesis of the bromide



(IV.)



(V.)



(VI.)

(V) is of great interest. It is the only known method for the preparation of spirocyclic arsonium salts in which the arsenic atom is linked solely to carbon atoms. Moreover, it is clear that, if the synthesis were repeated upon a derivative of *o*-xylylene dibromide having a suitable substituent in the benzene ring, the corresponding disubstituted analogue of the bromide (V) would possess molecular dissymmetry by virtue of the tetrahedral disposition of the four arsenic valencies, and thus be optically resolvable. The synthesis of such a salt will be investigated later.

If in the synthesis of the 2-methyl*iso*arsindoline (I, R = Me) only 1 equiv. of methyldichloroarsine is used, or if the refluxing is not sufficiently prolonged, distillation ultimately gives an unstable product which is almost certainly 2-*o*-(bromomethyl)benzyl*iso*arsindoline (VI); this crude product is readily soluble in hot alcohol, but the solution on boiling soon deposits the slightly soluble spiro-bromide (V). The latter compound can also be isolated from the undistilled residue in the distilling-flask. It would appear, therefore, that under the above conditions of preparation the initially formed 2-methyl*iso*arsindoline combines with unchanged dibromide, to give the arsonium bromide (IV). During the distillation, the latter loses methyl bromide, partly to give the *spiro*-bromide (V), which necessarily remains in the distilling flask, and partly to give the *iso*arsindoline (VI), which distils over. The identification of the crude unstable distillate as (VI) is confirmed by the facts that (*a*) the arsonium bromide (IV) is stable in boiling alcohol and therefore does not furnish the *spiro*-bromide (V) in these conditions, and (*b*) the *spiro*-bromide (V), being a salt, cannot be distilled, and its formation from the distillate must therefore occur during the boiling in alcohol.

In view of the isolation of arsenobenzene as a by-product in the preparation of 2-phenyl*iso*arsindoline, we have investigated its direct preparation. We find that sodium reacts spontaneously and vigorously with an ethereal solution of phenyldichloroarsine, furnishing arsenobenzene of high purity in 50% yield. (This reaction is in striking contrast to that given when *o*-xylylene dibromide also is present, in which case long heating and a catalyst are required to start the reaction.) *p*-Tolyldichloroarsine similarly furnishes arseno-*p*-toluene, $CH_3{\cdot}C_6H_4{\cdot}As{:}As{\cdot}C_6H_4{\cdot}CH_3$. The method of preparation is therefore clearly of considerable practical value.

The arsenobenzene was thus obtained as almost colourless crystals, stable in air, having m. p. 213—214° in a preheated apparatus, and a molecular weight of 917 in 0·44%, and 881 in 0·84%, boiling benzene solution, the theoretical molecular weight being 304.

Arsenobenzene has previously been prepared usually by reducing phenylarsonic acid with various reagents, although Blicke and Smith (*J. Amer. Chem. Soc.*, 1930, **52**, 2945) have prepared it by the three-days action of mercury on phenyldi-iodoarsine. The earliest recorded preparations clearly gave an impure product, described as yellow, and spontaneously inflammable in air. Even for apparently pure samples, wide ranges of m. p.'s and molecular weights have been recorded, as shown on p. 32 :

M. p.	*M.*	Solvent.	Reference.
196°	—	—	Michaelis and Schulte, *Ber.*, 1881, **14**, 912
212	399·8	Boiling C_6H_6	Michaelis and Schafer, *ibid.*, 1913, **46**, 1742
208	—	—	Binz, Bauer, and Hallstein, *ibid.*, 1920, **53**, 427
195	334	Boiling CS_2	Palmer and Scott, *J. Amer. Chem. Soc.*, 1928, **50**, 537
—	402	Boiling C_6H_6	,,
—	642	Freezing $C_{10}H_8$	,,
212—213	895, 915	Boiling C_6H_6	Blicke and Smith, *ibid.*, 1930, **52**, 2949
210—212	867	Boiling C_6H_6	Blicke and Powers, *ibid.*, 1933, **55**, 315

The recorded molecular weights in benzene are widely discordant, although our results approximate closely to the most recent values of Blicke and his co-workers (above) and indicate marked association. This association is shown by other similar compounds; *e.g.*, Steinkopf, Schmidt, and Smie (*Ber.*, 1926, **59**, 1463) have shown that the molecular weight of arsenomethane in solution corresponds to $(MeAs:)_5$, and they consider the compound to be actually pentamethyl*cyclo*pentarsine. It is clearly of great interest to determine whether arsenobenzene has the simple structure, PhAs:AsPh, and if so, whether it has the *cis*- or the *trans*-configuration, or whether it has a more complex (associated) structure. Dr. Edna M. Davidson has kindly submitted samples of our highly crystalline arsenobenzene to crystallographic and *X*-ray analysis. The compound proves, however, to have twelve PhAs: groups in the unit cell, and this complexity in particular has at present prevented the elucidation of its structure.

The therapeutic properties of the above *iso*arsindolines have been investigated by the staff of Imperial Chemical Industries Limited, who find that the arsine dihydroxide (II, X = OH), and therefore necessarily the oxide also, have noteworthy properties.* Preliminary trials have shown that this compound possesses slight activity against *Trypanosoma rhodesiense* and *T. cruzi* in mice, but greater activity against *T. congolense*. In view of this encouraging result, we are now preparing various substituted derivatives of the dihydroxide, and also its antimony analogue, in order to test their activity against *Trypanosoma* infection.

Experimental.

The names of solvents used for recrystallisation are given in parenthesis immediately after the compounds concerned.

2-Phenylisoarsindoline (I, R = Ph).—*o*-Xylylene dibromide (52·8 g.), phenyldichloroarsine (44·6 g., 1 mol.), and fine sodium wire (40 g., 8·6 atoms) were added in turn to dry ether (500 c.c.) in a 1-l. round-bottomed flask to which was fitted a reflux water-condenser, a dropping-funnel, and an inlet tube through which a current of pure nitrogen was passed throughout the experiment. The mixture was now refluxed for 11 hours, 5 c.c. of ethyl acetate being added at the beginning, and two further additions of 2·5 c.c. after 3 and 7 hours' boiling, respectively. After the third addition, the sodium, which had hitherto appeared almost unchanged, rapidly disintegrated. The mixture was allowed to cool, the nitrogen replaced by a stream of carbon dioxide, and the latter employed to force the solution through a sintered-glass filter into a small Claisen flask without exposure to air, the apparatus described by Holliman and Mann (J., 1943, 549) being used. After distillation of the ether, the dark brown residue was distilled at low pressure, and the crude *iso*arsindoline (I, R = Ph) obtained, b. p. 136—142°/0·3 mm.; 9·5 g., 18·5% calculated on the dibromide used. Redistillation gave a fraction, b. p. 136—138°/0·3 mm., but analysis showed that this fraction, even when repeatedly distilled, was impure. It was therefore cooled in ice-water and cautiously treated with concentrated nitric acid. Vigorous oxidation occurred, and the dark red oil which formed crystallised ultimately when the mixture was diluted with water and stirred. This solid product, recrystallised from very dilute nitric acid, gave the *hydroxy-nitrate* (II, X = NO_3) as colourless crystals (10 g.), m. p. 149—150° (efferv.) (Found: C, 49·8; H, 4·4; N, 4·5. $C_{14}H_{14}O_4NAs$ requires C, 50·2; H, 4·2; N, 4·2%). When the powdered nitrate was treated with cold 10% aqueous sodium hydroxide solution in excess, the oily dihydroxide separated but rapidly dissolved on the addition of water. The solution was thoroughly extracted with chloroform; removal of the solvent from the extract gave an oil which readily solidified. After drying, crystallisation from ethyl carbonate furnished the *2-phenylisoarsindoline dihydroxide* (II, X = OH), colourless crystals, m. p. 78—79° (Found: C, 57·5; H, 5·6. $C_{14}H_{15}O_2As$ requires C, 57·9; H, 5·2%). The dihydroxide is freely soluble in water and in most organic solvents. Other methods of preparation are given below. The dihydroxide, when confined in a vacuum over phosphoric oxide, slowly gave the *oxide* (III), m. p. 130—131° (Found: C, 61·6; H, 5·1. $C_{14}H_{13}OAs$ requires C, 61·8; H, 4·8%), which on exposure to the air rapidly re-formed the dihydroxide.

A solution of the dihydroxide (II, X = OH, 8·5 g.) in chloroform (50 c.c.) was mixed with water (100 c.c.) and concentrated hydrochloric acid (15 c.c.), potassium iodide (0·1 g.) added, and sulphur dioxide passed through the chloroform layer for 30 minutes. This layer was then separated, dried (sodium sulphate), and distilled; after removal of the solvent, the pure *2-phenylisoarsindoline* (II), b. p. 136—138°/0·3 mm., was obtained (Found: C, 65·5; H, 5·1; *M*, cryoscopically in 0·52% ethylene dibromide solution, 246. $C_{14}H_{13}As$ requires C, 65·6; H, 5·1%; *M*, 256).

The following points concerning the above preparation of the arsine must be noted. (i) The yield of the arsine decreases if the refluxing is continued for more than 11 hours in spite of the inert atmosphere. Distillation of the ethereal solution should preferably be performed immediately the refluxing is complete. (ii) Increasing the amount of the initial addition of ethyl acetate did not apparently accelerate the onset of the reaction. A period of 7—8 hours' refluxing seemed to be necessary before the reaction became pronounced (as shown by the state of the sodium): it then proceeded rapidly. (iii) Much solid material separated from the ethereal solution as the reaction proceeded. In addition to unchanged sodium and sodium halide, this consisted of the amorphous material formed by the action of the sodium on the *o*-xylylene dibromide (see previous paper) and of arsenobenzene. The mixture was therefore rapidly but cautiously sieved to remove fragments of sodium, and then added in small quantities to much cold water. The brown, amorphous, insoluble material was washed with water until no longer sticky, collected, dried (10 g.), and then twice recrystallised from benzene, in which the amorphous component was freely soluble. Arsenobenzene (*ca.* 0·5 g.) was thus obtained in very pale yellow needles, m. p. 213—214° in preheated bath (Found: C, 47·6; H, 3·4. Calc. for $C_{12}H_{10}As_2$: C, 47·4; H, 3·3%). (iv) After distillation of the crude arsine (I, R = Ph), the black sticky residue in the Claisen flask was twice extracted with hot acetic acid to remove the viscous component. The solid, insoluble residue, after repeated recrystallisation from benzene, also furnished pure arsenobenzene (*ca.* 0·2 g.). (v) When benzene was used instead of ether in the original reaction, the mixture became black during the refluxing, and no volatile product other than benzene could subsequently be obtained.

* Patent protection pending.

The arsine dihydroxide (II, X = OH) was further characterised : (*a*) the addition of concentrated hydrobromic acid to its aqueous solution gave the *hydroxy-bromide* (II, X = Br), colourless needles from dilute hydrobromic acid, or from alcohol by ether precipitation : m. p. 132—133° (preliminary softening) (Found : C, 47·5; H, 3·9. $C_{14}H_{14}OBrAs$ requires C, 47·6; H, 4·0%); (*b*) mixing of aqueous solutions of picric acid and the dihydroxide, or of warm alcoholic solutions of picric acid and the hydroxy-nitrate, gave the *hydroxy-picrate* (II, X = $C_6H_2O_7N_3$), yellow needles from alcohol, m. p. 164—166° (decomp.) (Found : C, 48·2; H, 3·1; N, 8·4. $C_{20}H_{16}O_8N_3As$ requires C, 47·9; H, 3·2; N, 8·4%).

Other Methods for the Preparation of the Arsine Dihydroxide (II, X = OH).—(A) *Bromine.* A solution of bromine (0·8 g., 1 mol.) in chloroform (7 c.c.) was slowly added to an agitated solution of the arsine (1·3 g.) also in chloroform (10 c.c.). The bromine was rapidly absorbed, and the white solid arsine dibromide was precipitated. A 5% aqueous solution of sodium hydroxide was now added, and the mixture shaken until the dibromide disappeared. The chloroform was separated and evaporated, and the viscous arsine dihydroxide which remained ultimately crystallised.

(B) *Chloramine-T.* Solutions of the arsine (2·5 g.) and of hydrated chloramine-T (2·8 g., 1 mol.), each in alcohol (100 c.c.), were mixed and refluxed for 2 hours, sodium chloride rapidly separating. The solution was then filtered and evaporated, and the oily residue, when triturated with anhydrous ether, deposited 2-*phenylisoarsindoline hydroxytoluene-p-sulphonamide* (II, X = $C_7H_7{\cdot}SO_2{\cdot}NH$), white crystals (ethyl carbonate), m. p. 122° (Found : C, 56·8; H, 5·2. $C_{21}H_{22}O_3NSAs$ requires C, 56·9; H, 5·0%). When this compound was decomposed by sodium hydroxide solution, chloroform readily extracted the liberated arsine dihydroxide. When cold alcoholic solutions of the sulphonamide and of picric acid were mixed, the above hydroxy-picrate was precipitated.

(C) *Hydrogen peroxide.* A solution of the arsine (1 g.) in acetone (20 c.c.) was diluted with " 20-volume " aqueous hydrogen peroxide (5 c.c.), and set aside overnight. Evaporation of the solvent then gave a residue of the arsine dihydroxide which readily solidified, particularly when seeded.

(D) *Potassium permanganate.* The arsine (1·5 g., 3 mols.) was added to a solution of potassium permanganate (0·6 g., 2 mols.) and anhydrous sodium carbonate (0·3 g.) in cold water (50 c.c.). Partial reduction of the permanganate occurred immediately on shaking, and gentle warming for a few minutes caused complete discharge of the permanganate colour. The presence of the arsine dihydroxide in the filtered solution was shown by adding nitric acid, which precipitated the above hydroxy-nitrate (II, X = NO_3; 0·8 g.). The low yield shows, however, that further oxidation had probably occurred.

Potassium persulphate and potassium dichromate in aqueous solution did not give a smooth conversion of the arsine into its dihydroxide. Furthermore, when air was bubbled through a solution of the arsine (1 g.) in alcohol (30 c.c.) for 8 hours at room temperature, subsequent evaporation of the solvent left a residue of almost unchanged arsine.

2-*Phenylisoarsindoline Sulphide* (as III).—A solution of the arsine dihydroxide (2·5 g.) in chloroform (20 c.c.) was saturated with hydrogen sulphide, filtered, and the solvent evaporated. The white solid residual *sulphide* (2·5 g.) gave needles (alcohol), m. p. 108° (Found : C, 58·3; H, 4·7; S, 11·1. $C_{14}H_{13}SAs$ requires C, 58·3; H, 4·6; S, 11·1%).

2-*Phenyl*-2-*methylisoarsindolinium Iodide.*—A solution of the arsine (I, R = Ph, 1 g.) in methyl iodide (8 g.) was refluxed for 15 minutes, a white solid rapidly separating. Excess of methyl iodide was evaporated off, and the residue recrystallised from alcohol, the *iodide* being obtained in magnificent, colourless needles, m. p. 189—191° (decomp.) (Found : C, 44·9; H, 4·0; I, 31·5. $C_{15}H_{16}IAs$ requires C, 45·2; H, 4·0; I, 31·9%). This iodide is freely soluble in cold water, and treatment of this solution with aqueous picric acid immediately gave the *picrate*, yellow crystals from alcohol, m. p. 122—123° (Found : C, 50·6; H, 3·8; N, 8·4. $C_{21}H_{16}O_7N_3As$ requires C, 50·5; H, 3·6; N, 8·4%).

2-*Methylisoarsindoline* (I, R = Me).—*o*-Xylylene dibromide (52·8 g.), methyldichloroarsine (48·3 g., 1·5 mols.), fine sodium wire (40 g., 8·6 atoms), and ethyl acetate (5 c.c.) were added in this order to ether (800 c.c.) in the apparatus already described for (I, R = Ph), and the mixture refluxed for 24 hours. Three further acetate additions (5 c.c. each) were made after 9, 17, and 21 hours' refluxing respectively. No apparent reaction occurred, however, until *ca.* 18 hours' refluxing, whereupon the sodium steadily disintegrated. The solution was then filtered and distilled in carbon dioxide as already described, two colourless fractions being obtained : (ii) b. p. 39°/17 mm., 4 g.; (ii) b. p. 115°/17 mm., 1·5 g. The latter was pure 2-*methylisoarsindoline* (Found : C, 56·2; H, 5·7. $C_9H_{11}As$ requires C, 55·7; H, 5·7%); yield 3·9%.

2 : 2-*Dimethylisoarsindolinium Iodide.*—A vigorous reaction occurred when the above arsine was refluxed with excess of methyl iodide, giving a white solid product. Recrystallisation of the latter from alcohol gave the crystalline *iodide*, m. p. 210—211° (slight darkening) (Found : C, 35·5; H, 4·4; I, 37·7. $C_{10}H_{14}IAs$ requires C, 35·7; H, 4·2; I, 37·8%). Mixing alcoholic solutions of this iodide and of picric acid precipitated the corresponding *picrate*, yellow needles from alcohol, m. p. 209° (Found : C, 43·8; H, 3·8; N, 9·8. $C_{16}H_{16}O_7N_3As$ requires C, 43·9; H, 3·7; N, 9·6%).

2-*o*-(*Bromomethyl*)*benzyl*-2-*methylisoarsindolinium Bromide* (IV).—Powdered *o*-xylylene dibromide (0·81 g., 1 mol.) was added to 2-methyl*iso*arsindoline (0·60 g.) in a small flask having a ground glass stopper. The closed flask was gently warmed until the mixture formed a homogeneous liquid, which, when cooled and stirred, solidified. These operations were performed with a minimum exposure to the air, because of the highly hygroscopic properties of the resulting *bromide* (IV). The latter was then pulverised under and thoroughly washed with dry ether, and finally dried in a vacuum over phosphoric anhydride (Found : C, 44·5; H, 5·0; Br, 35·0. $C_{17}H_{19}Br_2As$ requires C, 44·5; H, 4·2; Br, 34·9%). Recrystallisation of this bromide was not attempted : it was freely soluble in cold alcohol.

As-spiro-*Bisisoarsindolinium Bromide* (V).—The above bromide (IV) was heated in a small flask at 14 mm. pressure. At 50—60° fusion to a viscous liquid, with slight effervescence began, and as the temperature was slowly raised to 200°, this liquid became more mobile and darker, and after *ca.* 15 minutes at 200° it slowly crystallised. The cold product, when stirred with a small quantity of alcohol, gave colourless crystals of the spirocyclic *bromide* (V), which were then recrystallised from dilute aqueous hydrobromic acid (Found : C, 53·2; H, 4·5; Br, 21·9. $C_{16}H_{16}BrAs$ requires C, 52·9; H, 4·4; Br, 22·0%) : recrystallisation from water causes slight hydrolysis (Found : C, 54·1; H, 5·35; Br, 21·05%). The bromide on heating decomposes at 235—239° with effervescence; its low solubility in cold alcohol and lack of hygroscopic properties differentiate it sharply from the parent bromide (IV).

When hot aqueous solutions of the bromide (V) and of picric acid were mixed and cooled, the spirocyclic *picrate* separated; yellow crystals from alcohol, m. p. 188—189° (Found : C, 51·7; H, 4·0; N, 8·3. $C_{22}H_{16}O_7N_3As$ requires C, 51·7; H, 3·6; N, 8·2%). When a similar solution of the bromide (V) was treated with excess of aqueous potassium iodide, the spirocyclic *iodide* was immediately precipitated. It was collected, dissolved in hot water, reprecipitated with potassium iodide, and finally recrystallised from hot water; colourless crystals of indefinite m. p. (decomp. starts *ca.* 200°) (Found : C, 46·8; H, 4·2; I, 30·65. $C_{16}H_{16}IAs$ requires C, 46·8; H, 3·9; I, 30·95%). It is markedly less soluble than the bromide in both cold and hot water.

A repetition of the above preparation of 2-methyl*iso*arsindoline was attempted, the only changes being that methyldichloroarsine (32·2 g., 1 mol.) was used, and the refluxing was limited to 10 hours. The solution, when filtered and distilled as before, gave the following colourless fractions : (*a*) b. p. 32—36°/15 mm., 1·5 g.; (*b*) b. p. 40—104°/15 mm., *ca.* 0·2 g.; (*c*) b. p. 115—120°/0·4 mm., 5 g. Fraction (*a*) also had b. p. 133—135°/760 mm., and was unchanged methyldichloroarsine. Fraction (*b*) gave no reaction with methyl iodide and therefore did not contain tertiary arsine. Fraction (*c*) slowly solidified, and when recrystallised from alcohol furnished *o*-xylylene dibromide, m. p. 93—95°. The alcoholic mother-liquor was boiled and concentrated, and when cooled it deposited colourless crystals of the *spiro*-bromide

(V), m. p. 235—239° (decomp.), almost insoluble in cold alcohol and only moderately soluble in hot alcohol. Their identity was confirmed by conversion into the *spiro*-picrate, m. p. 188—189°, and by mixed m. p. determinations. The b. p. of fraction (*c*) precludes the presence of free 2-methyl*iso*arsindoline; this fraction must therefore have consisted of the unchanged dibromide, and of the tertiary arsine (VI), which in the boiling alcohol furnishes the *spiro*-bromide (V).

The black, sticky residue from the above fractional distillation was washed with acetone, and the pale brown, insoluble product then extracted with boiling water. The filtered aqueous extract on cooling deposited a small quantity of the crystalline *spiro*-bromide (V), which was also characterised by conversion into the *spiro*-picrate, m. p. 188—190°, mixed and unmixed.

Arsenobenzene.—Fine sodium wire (5 g.) was added to a solution of phenyldichloroarsine (44·6 g., 1 mol.) in dry ether (200 c.c.) contained in a flask carrying a reflux water-condenser and an inlet tube through which dry nitrogen was passed throughout the experiment. A vigorous reaction ensued, the ether boiling and much white solid separating. When this reaction had subsided, more sodium wire (15 g.; total addition, 4·3 atoms) was added, and the mixture refluxed for 5 hours, by which time most of the sodium had disintegrated, and the solution had become pale orange. The cold mixture was now shaken and filtered, so that unchanged sodium remained in the flask, whereas the white solid was collected on the filter. Small fragments of sodium in the white solid were removed by hand, and the solid then washed with water and dried. The crude arsenobenzene (15 g., 49%) thus obtained was stable in air and almost colourless; it was recrystallised from benzene or (preferably) ethyl acetate, forming colourless crystals, m. p. 213—214° if determined in a preheated apparatus (Found: C, 47·1; H, 3·0%).

Arseno-p-toluene.—This was prepared precisely as the arsenobenzene, but from *p*-tolyldichloroarsine (23·7 g., 1 mol.) and sodium (10 g., 4·3 atoms) in ether (200 c.c.). The crude product (8 g., 48%), recrystallised from ethyl acetate, gave very pale yellow crystals of arseno-*p*-toluene, m. p. 185·5—186·5° in a preheated apparatus (Found: C, 50·65; H, 4·5. Calc. for $C_{14}H_{14}As_2$: C, 50·6; H, 4·3%). It is noteworthy that Michaelis (*Annalen*, 1902, **320**, 301) originally gave m. p. 184° for this compound, but later Michaelis and Schafer (*loc. cit.*) found that material crystallised from chloroform had m. p. 184° and that from benzene had m. p. 202°; Blicke and Smith (*loc. cit.*) found m. p. 218—219°. It is impossible to say whether the discrepancy in these m. p.'s was due to the method of determination, to impurities, or to the compound's being possibly a mixture of geometric isomers.

Dr. E. M. Davidson reports on a sample of arsenobenzene prepared by the above method and recrystallised from ethyl acetate: "The compound exists in very pale yellow monoclinic prismatic crystals elongated along the *b* axis, showing straight extinction and high birefringence with β along *b*, and the optic axial plane (010). The sign of birefringence is probably positive, although the nature of the crystals made optical determinations difficult. The unit cell dimensions were determined by single-crystal oscillation photographs: $a = 24{\cdot}13$, $b = 6{\cdot}16$, $c = 12{\cdot}14$ A., $\beta = 111°$; axial ratio = 3·92 : 1 : 1·97. Cell volume = 1687 A.^{3}. Space-group is $P2_1/a$. Density (measured), 1·778; density (calc.), 1·782. Number of PhAs groups in the unit cell = 12. From the X-ray data there is nothing to distinguish between six molecules, each of formula PhAs:AsPh, in the unit cell, and, for example, a cyclic structure of formula $(PhAs)_6$ with two molecules in the unit cell. The positive sign of birefringence, if this can be confirmed, is in favour of the former."

We gratefully acknowledge the help we have received from Dr. E. M. Davidson and from the staff of Imperial Chemical Industries, Ltd.

THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 26th*, 1944.]

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12. *The Synthetic Application of* o-β-*Bromoethylbenzyl Bromide. Part IV. The Preparation of 2-Substituted* 1 : 2 : 3 : 4-*Tetrahydroisoquinolines.*

By FREDERICK G. HOLLIMAN and FREDERICK G. MANN.

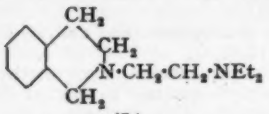
By the condensation of the above bromide with primary amines, a variety of 2-substituted 1 : 2 : 3 : 4-tetrahydro*iso*quinolines have been prepared, in which the 2-substituent is an alkyl, aryl, or a heterocyclic group. This reaction constitutes the only practical method by which such 2-aryl derivatives can be prepared.

Although the substituents chosen for this preliminary survey are those occurring in other compounds possessing marked physiological activity, the new tetrahydro*iso*quinolines do not reveal any outstanding therapeutic activity.

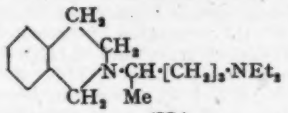
THE condensation of *o*-β-bromoethylbenzyl bromide with aromatic primary amines constitutes the only known practical method whereby 2-aryl-1 : 2 : 3 : 4-tetrahydro*iso*quinolines can be prepared (von Braun and Zobel, *Ber.*, 1923, **56**, 2142; Holliman and Mann, J., 1942, 737); a similar condensation also affords an excellent method for the preparation of 2-alkyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolines, for which, however, there are other, more laborious methods available (*cf.* Wedekind *et al.*, *Ber.*, 1901, **34**, 3986; 1903, **36**, 1161, 1167; 1909, **42**, 2138; von Braun and Wirtz, *Ber.*, 1927, **60**, 102; Buck *et al.*, *J. Amer. Chem. Soc.*, 1934, **56**, 1769; 1938, **60**, 2101; Allewelt and Day, *J. Org. Chem.*, 1941, **6**, 384). Since *o*-β-bromoethylbenzyl bromide is now readily available (Holliman and Mann, *loc. cit.*), we have made a variety of 2-substituted tetrahydro*iso*quinolines with a view to a rapid preliminary survey of their therapeutic activity. The *iso*quinolyl group is a component of many naturally occurring compounds having notable physiological activity; furthermore, Hjort, de Beer, and Fassett (*J. Pharm.*, 1938, **62**, 165; **63**, 253, 432; 1940, **68**, 69, 73) have found that several 2-alkyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolines lower the blood pressure considerably, and thus compare favourably with several natural and artificial drugs in their action as adrenaline-antagonisers.

We have selected for our initial experiments various substituents which in other compounds are associated with marked physiological action. *o*-β-Bromoethylbenzyl bromide reacted readily with *as-NN*-diethylethylenediamine to give ultimately the liquid 2-β-*diethylaminoethyl*-1 : 2 : 3 : 4-*tetrahydroisoquinoline* (I), characterised as its *dihydrobromide*, *dipicrate*, and *dimethiodide*. 2-Amino-δ-diethylamino-*n*-pentane similarly furnished 2-δ-*diethylamino*-α-*methyl*-n-*butyl*-1 : 2 : 3 : 4-*tetrahydroisoquinoline* (II), also characterised as

dihydrobromide and *dipicrate*: the compound (II) contains the alkyl side-chain which is present in plasmoquin and atebrin, and which is therefore intimately associated with their antimalarial properties.



(I.)



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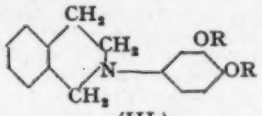
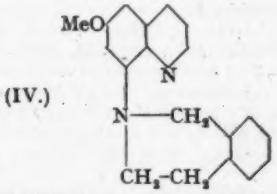
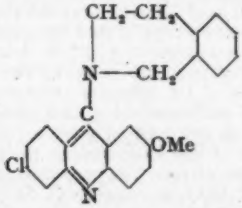


(III.)

For examples of 2-aryl derivatives, the bromide has been condensed with 3 : 4-dimethoxy- and 3 : 4-methylenedioxy-aniline in the presence of potassium carbonate, to furnish 2-(3′ : 4′-*dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydroisoquinoline* (III; R = Me) and the 2-(3′ : 4′-*methylenedioxyphenyl*) analogue (III; RR = $>CH_2$), respectively. No satisfactory product could be obtained by the attempted demethylation of (III; R = Me). The use of *p*-nitroaniline similarly furnished 2-(p-*nitrophenyl*)*tetrahydroisoquinoline*, from which a number of derivatives might readily be prepared.



(IV.)



(V.)

In order to obtain a compound allied in type to plasmoquin, the bromide was condensed with 8-amino-6-methoxyquinoline in the presence of alcoholic potassium carbonate, furnishing 6-methoxy-8-(2′-1′ : 2′ : 3′ : 4′-tetrahydro*iso*quinolyl)quinoline (IV), isolated as *monohydrochloride* and *monopicrate*.

An attempt to make compounds similarly allied in general type to atebrin has, however, demonstrated certain limitations attending the use of the dibromide for tetrahydro*iso*quinolyl formation. We have attempted to prepare 8-*chloro*-3-*methoxy*-5-(2′-1′ : 2′ : 3′ : 4′-*tetrahydroisoquinolyl*)*acridine* (V) by condensing the dibromide with 8-*chloro*-5-*amino*-3-*methoxyacridine*, but all attempts failed, in spite of a variety of conditions employed. The compound (V) was therefore prepared by the direct condensation of 1 : 2 : 3 : 4-tetrahydro-*iso*quinoline and 5 : 8-dichloro-3-methoxyacridine in boiling toluene, a method for which we are indebted to Dr. D. Muriel Hall of Bedford College (University of London); it was also obtained by heating these reagents with a mixture of phenol and potassium carbonate, but the yield was low owing to contamination with 8-chloro-5-phenoxy-3-methoxyacridine. The last method has, however, been successfully used to prepare the isomeric 8-*chloro*-3-*methoxy*-5-(1′-1′ : 2′ : 3′ : 4′-*tetrahydroquinolyl*)*acridine* from tetrahydroquinoline.

The therapeutic properties of these compounds have been investigated by the staff of Imperial Chemical Industries Ltd. (Biological Department) at Blackley. The compounds (I), (III; R = Me) and (III; RR = $>CH_2$) have been submitted to general tests, including a toxicity test in mice, a " chronic " toxicity test (*i.e.*, repeated dosage) in rats with subsequent examination of the organs, and a test on rabbit intestine: their effect on the blood pressure of the rabbit has also been examined. Toxicity was low, and the compounds did not reveal any outstanding physiological action. The dihydrobromide of (II), the hydrochloride of (IV), and the two acridines were tested for their action against *P. gallinaceum* infection in chicks, but were inactive.

Experimental.

2-β-*Diethylaminoethyl*-1 : 2 : 3 : 4-*tetrahydroisoquinoline* (I).—*as.-NN*-Diethylethylenediamine (3 c.c.; prepared by Mann's method, J., 1927, 2910) was added with stirring to powdered *o*-β-bromoethylbenzyl bromide (2·4 g.); a vigorous reaction, with much heat evolution, ensued. The cold glassy product, when heated with alcohol (40 c.c.), readily crystallised, a further crop separating as the mixture cooled. The united product, recrystallised from alcohol, furnished the *dihydrobromide* of (I), colourless crystals, m. p. 207—209° (Found: C, 46·2; H, 6·5; N, 7·0; Br, by Carius, 40·7; Br, ionic, 40·5. $C_{15}H_{24}N_2$, 2HBr requires C, 45·7; H, 6·6; N, 7·1; Br, 40·6%). Treatment of this compound with excess of picric acid, both in alcoholic solution, gave the *dipicrate* of (I), yellow crystals from alcohol–acetone, softening at 130°, m. p. 167—171° (decomp.) (Found: C, 47·3; H, 4·4; N, 16·4. $C_{15}H_{24}N_2.2C_6H_3O_7N_3$ requires C, 47·95; H, 4·35; N, 16·2%).

Basification of an aqueous solution of the dihydrobromide, followed by ether extraction and distillation, gave the *isoquinoline* (I) as a colourless mobile oil, b. p. 166—167°/14 mm. (Found: C, 77·8; H, 10·5; N, 12·2. $C_{15}H_{24}N_2$ requires C, 77·6; H, 10·3; N, 12·1%); this combined readily with methyl iodide, and the final sticky product solidified when triturated with ether; recrystallisation from alcohol furnished colourless crystals of the *dimethiodide* of (I), m. p. 183—185° (Found: C, 39·4; H, 6·05; N, 5·2. $C_{17}H_{30}N_2I_2$ requires C, 39·5; H, 5·8; N, 5·4%).

2-δ-*Diethylamino*-α-*methyl*-n-*butyl*-1 : 2 : 3 : 4-*tetrahydroisoquinoline* (II).—When 2-amino-5-diethylamino-*n*-pentane (4·9 g., 6·6 c.c.) was added to the bromide (8·4 g., 1 mol.) vigorous reaction ensued, which was controlled by external cooling. The cold, hygroscopic, glassy product was dissolved in hot alcohol, and ether added until the solution was turbid; slow cooling now gave crystals of the *dihydrobromide* of (II), which, after a repetition of the alcohol–ether treatment, had m. p. 190—192° with preliminary softening (Found: C, 49·4; H, 7·6; N, 6·5; Br, by Carius, 37·0; Br, ionic, 36·8. $C_{19}H_{36}N_2$, 2HBr requires C, 49·55; H, 7·3; N, 6·4; Br, 36·7%). Basification of an aqueous solution, followed by ether extraction, furnished the liquid *isoquinoline* (II), b. p. 200°/16 mm. (Found: C, 78·9; H, 11·4; N, 10·5. $C_{19}H_{30}N_2$ requires C, 78·8; H, 10·95; N, 10·2%).

The original preparation was repeated but with an excess (3 mols.) of the aminopentane. An ethereal extract of the cold reaction product was dried (potassium hydroxide), and on fractional distillation furnished the pure *iso*quinoline (II) directly.

Mixing of alcoholic solutions of (II) and of picric acid precipitated the sticky semi-solid *dipicrate*, which solidified on long boiling with alcohol, and was then recrystallised from alcohol–acetone; yellow leaflets, m. p. 150—151° (Found: C, 50·0; H, 5·5; N, 16·0. $C_{18}H_{20}N_2,2C_6H_3O_7N_3$ requires C, 49·2; H, 4·9; N, 15·3%). Methyl iodide reacted vigorously with the free base (II), but the deliquescent sticky product could not be crystallised.

No products similar in type to (I) and (II) could be isolated by the condensation of the dibromide with αγ-diamino-β-hydroxypropane or with *NN'*-di-(β-aminoethyl)ethylenediamine, $C_2H_4(NH{\cdot}C_2H_4{\cdot}NH_2)_2$.

2-(3′ : 4′-*Dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydroisoquinoline* (III; R = Me).—Pyrocatechol was methylated to veratrole by Ullmann's method (*Annalen*, 1903, **327**, 115), which was found to be much superior to that of Perkin and Weizmann (J., 1906, **89**, 1649). The nitration and subsequent reduction of veratrole were performed by Moureu's method (*Bull. Soc. chim.*, 1896, **15**, 647): Moureu decomposed the chlorostannate of the 3 : 4-dimethoxyaniline with hydrogen sulphide, but we found it advantageous to decompose this salt with aqueous sodium hydroxide, and extract the liberated amine repeatedly with ether. A powdered, intimate mixture of the bromide (15 g.), 3 : 4-dimethoxyaniline (8 g., 1 mol.), and potassium carbonate (12 g., 1·6 mols.) was heated in an oil-bath until effervescence began. The mixture was removed from the bath until the reaction subsided, and was then reheated at 130° for 30 minutes. An acetone extract of the cold pulverised product, when filtered and evaporated, gave a solid residue which, recrystallised from alcohol, furnished colourless needles of the *isoquinoline* (III; R = Me), m. p. 94—95° (Found: C, 76·0; H, 7·05; N, 5·3. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%). A mixture of this base (1·5 g.), hydriodic acid of constant b. p. (5 c.c.), and acetic acid (20 c.c.) was refluxed gently for 3 hours. The cold product when neutralised gave a sticky solid which could neither be crystallised nor converted into a crystalline picrate.

2-(3′ : 4′-*Methylenedioxyphenyl*)-1 : 2 : 3 : 4-*tetrahydroisoquinoline* (III; RR = $>CH_2$).—The 3 : 4-methylenedioxyaniline used was prepared from piperonal by the method of Rupe and Majewski (*Ber.*, 1900, **33**, 3401) (cf. Buck and Ide, *Org. Syn.*, 1935, **15**, 58). An intimate mixture of the bromide (2·8 g.), 3 : 4-methylenedioxyaniline (1·37 g., 1 mol.), and anhydrous sodium carbonate (4 g., 3·8 mols.) was heated at 130° for 15 minutes. An ethereal extract of the cold pulverised product when evaporated gave an oil (2·5 g., 99%) which rapidly solidified; recrystallisation from alcohol gave colourless needles of the *isoquinoline*, m. p. 58° (Found: C, 75·8; H, 6·0; N, 5·5. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 5·9; N, 5·5%). The *picrate* was prepared in and recrystallised from alcohol; m. p. 135° (Found: C, 54·8; H, 3·8; N, 11·5. $C_{16}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 54·8; H, 3·7; N, 11·6%).

2-(p-*Nitrophenyl*)-1 : 2 : 3 : 4-*tetrahydroisoquinoline*.—A mixture of the bromide (2·8 g.), *p*-nitroaniline (1·38 g., 1 mol.), and potassium carbonate (4 g., 2·9 mols.) was heated at 150° for 15 minutes; as the temperature rose to this value, no effervescence was detected, but steam was evolved at *ca.* 100° and the mixture darkened in colour at 110—120°. The final orange-coloured product was cooled, crushed, extracted with cold water, and the residue recrystallised from alcohol; the *isoquinoline* (1·2 g., 48%) was thus obtained as yellow plates, m. p. 152—154° (Found: C, 71·2; H, 5·7; N, 10·9. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·0%).

Alternatively, the above mixture was added to alcohol (20 c.c.) and refluxed for 6 hours. Hot alcohol (50 c.c.) was then added, and the product filtered off and extracted repeatedly with hot alcohol. The combined filtrate and washings were concentrated to *ca.* 50 c.c. and cooled; the *iso*quinoline (0·8 g.) crystallised on cooling, and when collected, washed with alcohol and water, and dried, was pure; m. p. 152—154°.

6-*Methoxy*-8-(2′-1′ : 2′ : 3′ : 4′-*tetrahydroisoquinolyl*)*quinoline* (IV).—A mixture of the bromide (8·4 g.), 8-amino-6-methoxyquinoline (4·8 g., 1 mol.), potassium carbonate (12 g.), and alcohol (120 c.c.) was refluxed for 6 hours, and then filtered whilst hot. The residue was washed with hot alcohol, and the united filtrates evaporated. The residual oil was dissolved in ether, the solution shaken with water and dried (sodium sulphate). After evaporation of the ether, fractional distillation gave an oil, b. p. 190—210°/0·05 mm., presumably the *iso*quinoline (IV). On cooling, however, it formed a glass which could not be crystallised; it was therefore dissolved in warm concentrated hydrochloric acid, and the solution on cooling deposited crystals of the *monohydrochloride* of (IV). This salt was collected, dried, and recrystallised from alcoholic ether, from which the *monohydrate* separated as hard yellowish-brown crystals, m. p. 145—147° (Found: C, 66·3; H, 6·2; N, 8·1; Cl, 10·2. $C_{19}H_{18}ON_2,HCl,H_2O$ requires C, 66·2; H, 6·1; N, 8·1; Cl, 10·3%). This hydrate possessed considerable thermal stability, and when heated at 100°/15 mm. for 5·5 hours lost only 70% of its water, which was slowly re-absorbed on exposure to cold air. The salt is only moderately soluble in cold water, and the solution develops a marked opacity, presumably by dissociation.

When an alcoholic solution of the above distillate was treated with alcoholic picric acid, a *monopicrate* was precipitated which was almost insoluble in boiling alcohol, but recrystallised from alcoholic acetone containing free picric acid as yellow crystals, m. p. 183° (decomp.) (Found: C, 58·8; H, 4·5; N. 14·8. $C_{19}H_{18}ON_2,C_6H_3O_7N_3$ requires C, 57·8; H, 4·05; N, 13·5%. $C_{19}H_{18}ON_2,2C_6H_3O_7N_3$ requires C, 49·7; H, 3·2; N, 15·0%).

8-*Chloro*-5-*amino*-3-*methoxyacridine*.—A current of dry ammonia was passed through a solution of 5 : 8-dichloro-3-methoxyacridine (2 g.) in phenol (5 g.) at 160° for 15 minutes. The semi-solid mass was cooled, triturated with ether, and the residual *aminoacridine hydrochloride* (2·7 g.) was collected, washed again with ether, and recrystallised from 50% aqueous alcohol; canary-yellow crystals, m. p. 349—350° (decomp.) (Found: C, 56·3; H, 4·0; N, 9·6. $C_{14}H_{11}ON_2Cl,HCl$ requires C, 56·95; H, 4·1; N, 9·5%).

A small excess of aqueous sodium hydroxide was added to a boiling alcoholic solution of this hydrochloride, and the whole was then poured into much water. The precipitated 8-*chloro*-5-*amino*-3-*methoxyacridine* was collected, washed with water, and purified by dissolution in much boiling alcohol, to which water was then cautiously added until a turbidity appeared; slow cooling deposited the acridine as yellowish-brown plates, m. p. 274° (Found: C, 64·6; H, 4·5; N, 10·6. $C_{14}H_{11}ON_2Cl$ requires C, 65·0; H, 4·25; N, 10·8%).

8-*Chloro*-3-*methoxy*-5-(2′-1′ : 2′ : 3′ : 4′-*tetrahydroisoquinolyl*)*acridine* (V).—Preliminary experiments showed that when an alcoholic solution containing equimolecular quantities of the bromide and 8-chloro-5-amino-3-methoxyacridine hydrochloride was refluxed with an excess of potassium carbonate for 6 hours, the acridine was unchanged. A dry mixture of the bromide (1·4 g.), the free amino-acridine (1·3 g., 1 mol.), and potassium carbonate (2 g.) was therefore heated at 140—150° for 10 minutes, by which time it had developed a reddish-brown colour but no effervescence was detected. The cold pulverised product was thoroughly extracted with cold water and alcohol in turn, but the yellow residue proved to be 8-*chloro*-5-*amino*-3-*methoxyacridine hydrobromide*; it was insoluble in all solvents tried, and before analysis was further washed first with boiling alcohol and then with hot water (Found: C, 50·2; H, 3·6; N, 8·6; Cl + Br, 32·6. $C_{14}H_{11}ON_2Cl,HBr$ requires C, 49·5; H, 3·5; N, 8·25; Cl + Br, 34·1%).

The acridine (V) was therefore prepared by the following methods. (A) A mixture of 5 : 8-dichloro-3-methoxyacridine (2·8 g.), 1 : 2 : 3 : 4-tetrahydro*iso*quinoline (2·8 g., 2 mols.) and toluene (40 c.c.) was refluxed for 36 hours, and the tetrahydro*iso*quinoline hydrochloride which had separated was filtered off from the hot solution. The filtrate on cooling deposited the *acridine* (V) (1·6 g.), which was recrystallised from alcohol; yellow crystals, m. p. 178—181° (Found: C, 73·5; H, 4·7; N, 7·7. $C_{23}H_{19}ON_2Cl$ requires C, 73·7; H, 5·05; N, 7·5%).

(B) A mixture of the dichloroacridine (2·8 g.) and phenol (12 g.) was heated on a water-bath until a solution was obtained. Potassium carbonate (0·7 g.) and the *iso*quinoline (1·33 g., 1 mol.) were added in turn. Carbon dioxide was vigorously evolved, and the mixture became orange. After 2 hours' heating, the cold product was poured with vigorous

stirring into 10% aqueous sodium hydroxide solution. The aqueous layer was decanted, and the semi-solid residue, when triturated with ether, gave a yellow powder (2·1 g.). This was collected, washed with alcohol and water, and dried. Recrystallisation from alcohol and then from ethyl acetate ultimately gave the pure acridine (V), m. p. 179—180°, unchanged by admixture with that prepared by method (A). Several similar experiments showed that the crude product obtained by method (B) was contaminated with the intermediate 8-chloro-5-phenoxy-3-methoxyacridine, the presence of which necessitated the repeated and wasteful recrystallisation. Method (B) is essentially that developed by Burckhalter, Jones, Holcomb, and Sweet (*J. Amer. Chem. Soc.*, 1943, **65**, 2012).

8-Chloro-3-methoxy-5-(1′-1′ : 2′ : 3′ : 4′-tetrahydroquinolyl)acridine.—This preparation was precisely similar to (B) above, but utilised 1 : 2 : 3 : 4-tetrahydroquinoline (1·33 g.). After the mixture had been heated on the water-bath for 3 hours, it was cooled and poured with stirring into 10% aqueous sodium hydroxide (60 c.c.). The red, viscous, insoluble solid was now extracted with ether (in which it was readily soluble), and the extract thoroughly washed with very dilute acetic acid and then with water, and finally dried (sodium sulphate). After complete removal of the ether, the residue readily solidified, and after recrystallisation from alcohol furnished yellow crystals (1·7 g.) of the above *acridine*, m. p. 169—171° (Found : C, 73·75; H, 5·4; N, 7·25%). The omission of potassium carbonate from the original reaction mixture caused a marked decrease in the yield of the acridine.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 6th*, 1944.]

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13. *The Synthetic Application of* o-β-*Bromoethylbenzyl Bromide. Part V. The Preparation and Properties of Thioisochroman, Selenoisochroman, Telluroisochroman, and of their Optically Active Derivatives.*

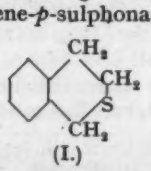
By FREDERICK G. HOLLIMAN and FREDERICK G. MANN.

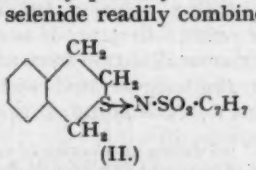
The three *iso*chromans named above have been prepared by the interaction of *o*-β-bromoethylbenzyl bromide and sodium sulphide, selenide, and telluride, respectively. The heterocyclic ring in these compounds has considerable stability, and hence they possess many of the normal chemical properties of alkyl sulphides, selenides, and tellurides.

Each of these compounds has been combined with *p*-chlorophenacyl bromide to give the corresponding sulphonium, selenonium, and telluronium salts, in which the Group VI element has become 3-covalent and asymmetric; consequently each salt has been resolved *via* the bromocamphorsulphonates, and the optically active picrates isolated. 2-p-*Chlorophenacylthioisochromanium picrate*, $[M]_D$ −242° and +250°, and the corresponding *seleno-picrate*, $[M]_D$ −533° and +504°, have thus been obtained; they possess very high optical stability. 2-p-*Chlorophenacyltelluroisochromanium picrate* has not been isolated in optically pure condition, but the optically impure enantiomorphs have been isolated having $[M]_D$ −632° and +578° : evidence is adduced that the optically pure picrate would have $[M]_D$ >750°. These telluronium salts are much less stable optically than the corresponding sulphonium and selenonium salts, and racemise moderately rapidly in boiling solvents; even so, however, the *l*-telluronium picrate in acetone solution at room temperature required *ca.* 20 days for complete racemisation. The markedly increasing rotation of the above salts, taken in the order of the sulphur, selenium, and tellurium members, is noteworthy.

The significance of these results is briefly discussed.

It has been shown by von Braun and Zobel (*Ber.*, 1923, **56**, 2142) that *o*-β-bromoethylbenzyl bromide reacts with sodium sulphide to furnish the liquid thio*iso*chroman (I), which they characterised as the crystalline methiodide. We find that the bromide reacts similarly with alcoholic sodium selenide and telluride, forming the crystalline analogues, *seleno*iso*chroman* and *telluro*iso*chroman*. The heterocyclic ring in each of these three compounds has considerable stability, and in this respect resembles the corresponding ring in the 2-substituted 1 : 2 : 3 : 4-tetrahydro*iso*arsinolines (Holliman and Mann, J., 1943, 547); consequently these compounds show the normal reactions of sulphides, selenides, and tellurides, respectively. Thus, the selenide and the telluride also combine readily with methyl iodide to give highly crystalline *methiodides*. The sulphide (I) combines with sodio-toluene-*p*-sulphonchloroamide (chloramine-T), furnishing *thio*iso*chroman*-p-*toluenesulphonylimine* (II), whereas the selenide, similarly treated, ultimately furnishes *seleno*iso*chroman oxide* (III) and toluene-*p*-sulphonamide, although these compounds may possibly unite in solution to form the unstable hydroxyselenonium toluene-*p*-sulphonamide. The selenide readily combines with chlorine and with bromine to give


(I.)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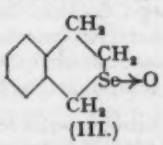
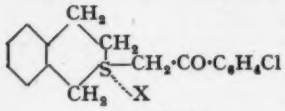

(III.)

the crystalline *seleno*iso*chroman dichloride* and *dibromide*, respectively; these are stable compounds which can be recrystallised unchanged from alcohol, but the dibromide, when treated with silver oxide or sodium hydroxide, is hydrolysed to the selenoxide (III). The telluride combines similarly with bromine to give the stable *telluro*iso*chroman dibromide*. Although the selenoxide (III) is a crystalline compound, m. p. 104—105°, it slowly decomposes, even in a vacuum at room temperature, furnishing the parent selenide and other products; this type of decomposition is shown by many selenoxides (cf. Gaythwaite, Kenyon, and Phillips, J., 1928, 2287; Edwards, Gaythwaite, Kenyon, and Phillips, *ibid.*, p. 2293; Foster, *Rec. Trav. chim.*, 1935, **54**, 447).

Although dissymmetric selenoxides, of the type abSe→O, should, by analogy with the corresponding sulphoxides, be resolvable into optically active forms, no such resolution has yet been achieved (Gaythwaite,

Kenyon, and Phillips, *loc. cit.*). Our selenoxide (III) combines readily with *d*-bromocamphorsulphonic acid, forming the crystalline 2-*hydroxyselenoisochromanium* d-*bromocamphorsulphonate*, which is considerably more stable than the parent selenoxide; fractional recrystallisation of this salt from ethyl acetate did not, however, furnish any evidence of optical resolution.

The main interest in the new series of heterocyclic compounds of type (I) lies, however, in the chemical and optical properties of the salts which they form with alkyl halides and which contain the 3-covalent Group VI element. We have previously shown that salts formed by the addition of *p*-chlorophenacyl bromide have usually a greater stability than those formed with simple alkyl or phenacyl halides (Holliman and Mann, J., 1943, 550). Consequently, we have combined the three compounds of type (I) with *p*-chlorophenacyl bromide, to furnish respectively the highly crystalline 2-p-*chlorophenacyl-thio-*, *-seleno-*, and *-telluro-*iso*chromanium bromides* (cf. IV; X = Br). Each of these compounds contains an asymmetric 3-covalent Group VI element, and we have investigated their resolution and optical properties for two reasons. First, a eutropic series * of three optically active compounds had not previously been obtained, and a comparison of their optical properties was of obvious interest. Secondly, their optical stability is dependent on at least two factors, and might well be low. Racemisation of a dissymmetric arsonium salt, *e.g.*, 2-phenyl-2-*p*-chlorophenacyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinolinium iodide (Holliman and Mann, *loc. cit.*), must depend solely on the formation of a "dissociation equilibrium," [abcdAs]I $\rightleftarrows$ abcAs + dI; the arsonium ion itself, therefore, cannot racemise if it possesses high chemical stability. Our sulphonium salt (IV) and its analogues could, however, racemise either by the formation of a similar dissociation-equilibrium, of type [abcS]I $\rightleftarrows$ abS + cI, or by the direct racemisation of the cation itself: if the ring system of (IV) is regarded as being in the plane of the paper, the *p*-chlorophenacyl group must be above or below this plane, and simple oscillation of this group between these positions would involve racemisation. Racemisation due to this cause has no counterpart in the quaternary ammonium and arsonium salts.



(IV.)

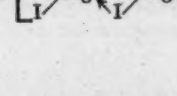
2-*p*-Chlorophenacylthio*iso*chromanium bromide (IV; X = Br) was therefore converted into the d-*bromocamphorsulphonate* (IV; X = $C_{10}H_{14}O_4BrS$) which, after twelve recrystallisations from alcohol, was optically pure *l*-sulphonium *d*-sulphonate, having $[M]_D$ −13·1° in methyl alcohol; this compound possessed moderately high optical stability, since one hour's boiling in methyl-alcoholic solution reduced the activity only to $[M]_D$ −11·0°. This sulphonate was converted into the optically pure l-*thio*iso*chromanium picrate* (IV; X = $C_6H_2O_7N_3$), having $[M]_D$ −242° in acetone solution. The activity of this picrate in acetone solution remained unchanged at room temperature for 24 hours; when the solution was heated under reflux, the activity fell to $[M]_D$ −232° after 1·25 hours and to $[M]_D$ −219° after 7·5 hours. The activity was unchanged when the picrate was rapidly recrystallised from boiling methyl or ethyl alcohol, but fell to $[M]_D$ −219° when a methyl-alcoholic solution was heated under reflux for one hour. The picrate therefore possesses a high degree of optical stability, but it should be noted that a "dissociation-equilibrium" (which would have involved the formation of *p*-chlorophenacyl picryl ether) could not occur in this compound, and loss of activity could have been caused therefore solely by direct racemisation of the cation.

The bromide (IV, X = Br) was similarly converted into the *l*-bromocamphorsulphonate, which on recrystallisation furnished the d-*sulphonium* l-*bromocamphorsulphonate*, and this in turn afforded the optically pure d-*thio*iso*chromanium picrate*, having $[M]_D$ +250° in acetone solution.

The 2-*p*-chlorophenacylseleno*iso*chromanium bromide was similarly converted into the *d*-bromocamphorsulphonate, which after only seven recrystallisations from alcohol furnished the optically pure l-*selenonium* d-*bromocamphorsulphonate* having $[M]_D$ −271° in ethyl alcohol and $[M]_D$ −293° in methyl alcohol; neither solution showed any change in rotation at room temperature for 24 hours, but heating under reflux of a methyl-alcoholic solution for 1 hour caused a reduction in rotation to $[M]_D$ −213°. The *d*-bromocamphorsulphonate in turn gave the optically pure l-*selenonium picrate*, having $[M]_D$ −533° in acetone solution. This picrate showed remarkable optical stability: its solution, in dry or in aqueous acetone, showed no change in rotation at room temperature for 2 days. Its rotation, in dry acetone solution, fell only to $[M]_D$ −518° after 30 minutes' and to $[M]_D$ −465° after 7·5 hours' heating under reflux; in aqueous acetone, it fell to $[M]_D$ −479° after 1 hour's refluxing. The rotation was unaffected by recrystallisation from methyl alcohol.

The *d*-bromocamphorsulphonate, when similarly treated with potassium mercuri-iodide, afforded the crystalline l-*selenonium mercuritri-iodide* (as IV; X = HgI_3); † this salt was slightly less optically stable than

* The term "eutropic series of compounds" we define as a series of compounds consecutive members of which differ only in that they contain consecutive elements of any one sub-group of the Periodic Classification; for example, PCl_5, $AsCl_3$, $SbCl_3$, $BiCl_3$. There is an obvious need for a term to describe such a series. Tutton ("Crystalline Form and Chemical Constitution," 1926, 127) first used the term, without clear definition, apparently to denote a series of compounds such as we have defined that were in addition isomorphous; Drew and Landquist (J., 1935, 1480) later used the term "eutropic series" to denote consecutive elements in one sub-group of the Periodic Classification.

† The molecular rotation of this salt has been calculated throughout on the basis that it has the general formula $[a_3Se][HgI_3]$, this being commonly assumed for similar sulphonium and selenonium salts (cf. Balfe, Kenyon, and Phillips, J., 1930, 2554; Cavell and Sugden, *ibid.*, p. 2572). The work of Evans, Mann, Peiser, and Purdie (J., 1940, 1209) indicates, however, that the anion must have the bivalent structure  , and the usual formula of these salts should therefore be doubled.

the picrate, since the rotation of an acetone solution, having initially $[M]_{5780}$ −421°, fell to $[M]_{5780}$ −352° after 9 days at room temperature.

The seleno*iso*chromanium bromide was also converted into the *l*-bromocamphorsulphonate, which on recrystallisation furnished the optically pure d-*selenonium* l-*sulphonate*, having $[M]_D$ +291° in methyl alcohol, and this salt in turn furnished the d-*selenonium picrate*, having $[M]_D$ +504° in acetone solution.

The only other known optically active selenium compound is phenylmethylselenetine platinichloride, which Pope and Neville (J., 1902, **81**, 1552) isolated in *d*- and *l*-forms, having $[M]_D$ +55·0° and −54·3°, respectively, in acetone solution.

2-*p*-Chlorophenacyltelluro*iso*chromanium bromide is markedly less stable chemically than its sulphur and selenium analogues, and when boiled with aqueous alcohol slowly gives the *telluroisochroman hydroxybromide* and *p*-chloroacetophenone. The bromide in methyl-alcoholic solution was converted into the d-*bromocamphorsulphonate*, which was isolated by complete evaporation of the solution at room temperature; the residue, when first extracted with cold alcohol and then recrystallised from hot alcohol, furnished the optically impure l-*telluronium* d-*bromocamphorsulphonate*, the optically purest sample thus isolated having $[M]_D$ −99° in methyl-alcoholic solution. The cold alcoholic extract, when again evaporated to dryness and extracted with petrol, furnished a residue of the optically impure *d*-telluronium *d*-bromocamphorsulphonate; in this case, the optically purest sample isolated had $[M]$ +579° in methyl-alcoholic solution. These *d*-bromocamphorsulphonates in cold methyl- and ethyl-alcoholic solution exhibited slow mutarotation, which became rapid when the solutions were boiled. Consequently, although the solubilities of the two diastereoisomerides in cold ethyl alcohol were markedly different, even rapid recrystallisation of the *l*-telluronium *d*-sulphonate from alcohol gave only small progress towards the isolation of the optically pure salt; when it became clear that this isolation would involve excessive material and labour it was abandoned.

The mutarotation of this bromocamphorsulphonate in cold solvents presents some interesting features. Lowry and Gilbert (J., 1929, 2867) have shown that the mutarotation of *l*-phenyl-*p*-tolylmethyltelluronium *d*-bromocamphorsulphonate in cold acetone and ethyl acetate did not even approximate to a unimolecular reaction, a fact for which they were unable to suggest an explanation. (Their demonstration that the racemisation of the corresponding iodide was also not unimolecular may, however, have been vitiated by the speed of the racemisation and the experimental difficulties under which it was observed.) We find that the mutarotation of our *l*-telluronium *d*-bromocamphorsulphonate is also not unimolecular: this is clearly shown by the following values for the reaction coefficient (calculated as that of a unimolecular reaction, and expressed as hours^{-1} $\log_{10}$) of a 0·987% methyl-alcoholic solution of the chemically pure but optically impure salt thermostatically controlled at 22°, the first reading ($t = 0$) being made 18 minutes after the initial dissolution of the salt:

t (hrs.).	α_D.	$[M]_D$.	$k \times 10^4$.	t (hrs.).	α_D.	$[M]_D$.	$k \times 10^4$.	t (hrs.).	α_D.	$[M]_D$.	$k \times 10^4$.
0·00	−0·18°	−32·2°	—	3·25	+0·54°	+ 97·0°	663	13·75	+1·34°	+241°	552
0·25	−0·08	−14·4	972	4·25	+0·66	+119	623	16·75	+1·42	+255	528
0·50	0·00	0·00	894	5·50	+0·81	+146	610	20·75	+1·51	+271	525
0·75	+0·06	+10·8	808	6·75	+0·94	+169	604	24·75	+1·59	+286	573
1·25	+0·19	+34·1	780	8·25	+1·07	+192	599	28·75	+1·61	+289	545
1·75	+0·30	+53·9	750	9·75	+1·15	+207	572	35·75	+1·65	+296	515
2·50	+0·41	+73·7	671	11·75	+1·26	+226	564	48·75	+1·66	+298	—
								71·50	+1·66	+298	—

We have obtained similar results for other samples both of the *l*-telluronium and of the more soluble *d*-telluronium *d*-bromocamphorsulphonate. If the change which is occurring in our compound (and in Lowry and Gilbert's) is solely optical, *i.e.*, is unaccompanied by any chemical change, this departure from the unimolecular reaction is extremely difficult to interpret. After the mutarotation of our salt was complete, the solution was evaporated to dryness at room temperature, and (even after prolonged drying) the residue was no longer analytically quite pure. It is possible, therefore, that the course of the mutarotation was affected by interaction of the cation with the solvent or with impurities therein (*e.g.*, traces of water). We hope to examine this point in greater detail later, as the large but slow change in rotation of our salt, and of the corresponding picrate described below, makes them particularly suitable for mutarotation studies, and a fundamental point in the stereochemistry of tellurium may be involved. There is little doubt that the heterocyclic system in our cation is chemically unchanged during the mutarotation; on the other hand, the *p*-chlorophenacyl group can react with water and might conceivably react also with alcohols or ketones, and consequently mutarotation studies in solvents other than these are clearly required.

By treating the *l*-telluronium *d*-sulphonate with sodium picrate in methyl alcohol, the l-2-p-*chlorophenacyltelluroisochromanium picrate* was readily precipitated; its rotation depended on the optical purity of the parent sulphonate and on the subsequent treatment of the picrate, but the optically purest sample we have isolated had $[M]_D$ −632° in acetone solution. By estimating the proportion of inactive material in such a sample, the rotation of the remainder can be calculated as $[M]_D$ *ca.* −750° (see p. 44), and there is reason to believe that the rotation of the optically pure picrate is even higher.

The *d*-telluronium *d*-sulphonate, which was never isolated in as optically pure a condition as its less soluble diastereoisomeride, furnished the *d*-picrate, the highest rotation of which we found to be $[M]_D$ +575°.

The *l*-telluronium picrate underwent very slow racemisation in acetone solution at room temperature, the

complete process requiring *ca.* 20 days. The reaction constant of this racemisation was determined with several samples of the picrate, and showed that this process also was not a unimolecular reaction. In this case again, however, analysis of the recovered picrate showed that it was no longer quite pure: it is significant that the speed of racemisation was increased markedly by the presence of a small proportion of water in the acetone, and the course of the above racemisation may well have been influenced by some concurrent slight chemical reaction.

The magnitude of the rotation, and the comparative optical stability of our telluronium picrate are in striking contrast to those of Lowry and Gilbert's telluronium iodide (*loc. cit.*), the only other telluronium salt of type [abcTe]X to be obtained optically active; the maximum rotation recorded for their iodide in ethyl acetate was $[M]_{5461}$ −67° and +34°, and the longest period required for complete racemisation was *ca.* 30 minutes. Their salt, being a methyltelluronium iodide, would however undoubtedly be particularly liable to partial dissociation in solution, and its racemisation, unlike that of our telluronium picrate, might have been due both to this dissociation and to direct racemisation of the telluronium cation:

The considerable difficulties attending the isolation of our telluronium salt in an optically pure condition have prevented an accurate comparison of the optical properties of the three eutropic sulphonium, selenonium, and telluronium salts, although the considerable increase in the rotation of these salts, taken in this order, is unmistakable, and represents a factor in a eutropic series that has not previously been demonstrated. Even if the optically pure telluronium salt had been isolated, however, this comparison of the optical properties would have been very limited in scope, because the comparatively low solubilities of our bromocamphorsulphonates restricted their conversion, by double decomposition in solution, into the even less soluble picrates and mercuritri-iodides, *i.e.*, into coloured salts the measurement of whose rotatory dispersion must necessarily have been limited to a very short range of wave-length. For our original purpose, salts that were both colourless and optically stable were clearly required. Furthermore, it would have been of great interest if the bromides or iodides of our optically active sulphonium, selenonium, and telluronium cations could have been isolated for comparison of their optical stabilities in solution, since these salts, unlike our picrates, might undergo racemisation by dissociation in solution and/or direct racemisation of their optically active cations.

Experimental.

All rotations were measured in a 4-dm. tube. Unless otherwise stated, the rotations were measured at 16° ± 1°, with the sodium-D line, $\lambda = 5893$, as the source of light. The reaction coefficient k has in all cases been calculated as that of a unimolecular reaction, and expressed in hours^{-1} $\log_{10}$.

Thioisochroman (I).—This was prepared by the following modification of von Braun and Zobel's method (*loc. cit.*). Sodium sulphide nonahydrate (36 g., 1·7 mols.) was added to a solution of *o*-β-bromoethylbenzyl bromide (25 g., 1 mol.) in alcohol (250 c.c.), and the mixture heated under reflux on a water-bath for 2 hours, the alcohol then being distilled off. The cold semi-solid residue was treated with water and twice extracted with ether. The combined extracts were washed with water, dried (calcium chloride), and distilled, the thio*iso*chroman being isolated as a colourless liquid, b. p. 128—130°/15 mm., having a characteristic odour; 7·6 g., 56%. It readily formed the methiodide, m. p. 124° (efferv.) (Found: C, 41·0; H, 4·3. Calc. for $C_{10}H_{13}IS$: C, 41·1; H, 4·45%); von Braun and Zobel give m. p. 123°.

Thioisochromantoluene-p-*sulphonylimine* (II).—This readily crystallised when (I) was shaken with an excess of a cold aqueous solution of chloramine-T: colourless crystals from alcohol, m. p. 165° (Found: C, 60·4; H, 5·5; N, 4·5. $C_{16}H_{17}O_2NS_2$ requires C, 60·2; H, 5·3; N, 4·4%).

dl-2-p-*Chlorophenacylthioisochromanium Bromide* (IV, X = Br).—A mixture of equimolecular quantities of (I) and of *p*-chlorophenacyl bromide was continuously stirred whilst it was gently heated; as the temperature reached *ca.* 100°, the clear liquid rapidly crystallised. The cold product, recrystallised from water (charcoal), furnished the *monohydrate* of the bromide, m. p. 130° (Found: C, 50·8; H, 4·4; Cl, 8·8; Br, 19·9. $C_{17}H_{16}OClBrS,H_2O$ requires C, 50·8; H, 4·5; Cl, 8·8; Br, 19·9%). A hot alcoholic solution of the bromide, treated with an excess of aqueous sodium picrate, gave on cooling the corresponding dl-*picrate* (IV, X = $C_6H_2O_7N_3$), yellow crystals from alcohol, m. p. 175—175·5° (Found: C, 52·3; H, 3·5; N, 8·5. $C_{23}H_{16}O_9N_3ClS$ requires C, 51·9; H, 3·4; N, 7·9%).

Resolution of the 2-p-*Chlorophenacylthioisochromanium Ion.*—Solutions of the above bromide (46·5 g.) and of silver *d*-bromocamphorsulphonate (56·0 g., 1 mol.), each in a hot mixture of alcohol (300 c.c.) and water (60 c.c.), were mixed, boiled, filtered, and the alcohol then cautiously removed under reduced pressure. The cold residue consisted of a heavy oil and some water; the latter was decanted, and the oil, when triturated with alcohol (50 c.c.), readily furnished the crude crystalline sulphonium *d*-bromocamphorsulphonate, which was collected, washed with alcohol (50 c.c.) and ether, and dried; 36 g. Twelve recrystallisations from alcohol gave the optically pure l-*sulphonium* d-*bromocamphorsulphonate* (IV, X = $C_{10}H_{14}O_4BrS$), m. p. 168—170° (Found: C, 52·5; H, 5·1; S, 10·3. $C_{27}H_{30}O_5ClBrS_2$ requires C, 52·8; H, 4·9; S, 10·4%), α −0·10°, $[M]$ −13·1° (*c*, 1·172% in methyl alcohol). This rotation was not detectably changed by two more crystallisations from alcohol. Although the above resolution was performed in ethyl alcohol, rotations were determined in methyl alcohol because of the greater solubility of the salt in this solvent. A solution of the salt (0·2916 g.) in methyl alcohol (10 c.c.) was refluxed for 1 hour, cooled, and made up to 30 c.c. (*i.e.*, 0·972%); it then had α −0·07°, $[M]$ −11·0°, a very small degree of mutarotation having therefore occurred.

l-2-p-*Chlorophenacylthioisochromanium Picrate.*—Methyl-alcoholic solutions of the above sulphonate (14 times recrystallised) and of sodium picrate were cooled to 0° and mixed; the l-*picrate*, which was rapidly precipitated, was collected, washed in turn with methyl alcohol, water and methyl alcohol, and dried (Found: C, 52·4; H, 3·6; N, 8·3. $C_{23}H_{16}O_9N_3ClS$ requires C, 51·9; H, 3·4; N, 7·9%); m. p. 170—171°, α −0·60°, $[M]$ −242° (*c*, 0·330% in acetone). To check the completeness of the above resolution, the mother-liquor from the fourteenth recrystallisation of the sulphonate was similarly treated with sodium picrate; the *l*-picrate thus obtained had α −1·26°, $[M]$ −243° (*c*, 0·687% in acetone).

The rotation of this picrate remained unchanged when the salt was recrystallised from methyl or ethyl alcohol, and when its acetone solution was set aside at room temperature for 24 hours at 16°. In the following experiments, the picrate used in (*a*) and (*b*) had initially $[M]$ −243°; that in (*c*), $[M]$ −233°. (*a*) A solution of the picrate (0·1776 g.) in acetone (10 c.c.) was refluxed for 1·25 hours, cooled, and made up to 30 c.c. The solution (0·592%) then had α −1·04°, $[M]$ −232°. (*b*) Experiment (*a*) was repeated, with 7·5 hours' heating of the picrate (0·2076 g.). The final solution (0·692%) had α −1·14°, $[M]$ −219°, racemisation having proceeded to *ca.* 5%. (*c*) A 0·8% methyl-alcoholic solution of the picrate

was refluxed for 1 hour, and the solvent then removed in a desiccator at room temperature. A 0·660% acetone solution of the residual picrate had α −1·09°, $[M]$ −219°.

The d-*thio*isochromanium l-*bromocamphorsulphonate* was similarly prepared from the *dl*-bromide and silver *l*-bromocamphorsulphonate. After twelve recrystallisations from ethyl alcohol, a 1·189% methyl-alcoholic solution had α +0·12°, $[M]$ +15·5°, and after fourteen such recrystallisations, a 1·180% methyl-alcoholic solution had α +0·12°, $[M]$ +15·6°; the final crop (Found: C, 52·55; H, 5·3%) had m. p. 168—170°, depressed to 135—144° by admixture with the *l*-sulphonium *d*-bromocamphorsulphonate.

d-2-p-*Chlorophenacylthio*isochromanium *picrate* was prepared from the *l*-sulphonate by the method previously described; yellow crystals (Found: C, 51·8; H, 3·4; N, 7·8%), m. p. 168—169° with preliminary softening; α +1·26°, $[M]$ +250° (*c*, 0·671% in acetone).

*Seleno*isochroman.—The following method is an adaptation of that used by Morgan and Burstall (J., 1929, 1096) for seleno*cyclo*butane. Sodium (7 g.) was slowly added to alcohol (250 c.c.) contained in a 3-necked flask carrying a reflux water-condenser and two delivery tubes, only one of which reached to the bottom of the flask. When dissolution of the metal was complete, the mixture was cooled and diluted with water (6 c.c.). Hydrogen selenide, prepared by the action of dilute sulphuric acid on aluminium selenide (20 g.), was then bubbled through the solution whilst a vigorous current of hydrogen was passed through the shorter tube over the solution to prevent oxidation of the sodium selenide, which separated as a white powder. *o*-β-Bromoethylbenzyl bromide (25 g.) was then added, and the mixture refluxed for 3 hours, the rapid stream of hydrogen being maintained meanwhile. The alcohol was then distilled off, and the residue treated with water, and finally thoroughly extracted with ether. The extract was washed with water, dried (calcium chloride), and distilled, the *seleno*isochroman being obtained as a very pale yellow liquid, b. p. 150°/18 mm. (10·2 g., 58%), which rapidly crystallised; colourless crystals from methyl alcohol, m. p. 46—47° (Found: C, 54·5; H, 5·3. $C_9H_{10}Se$ requires C, 54·8; H, 5·1%). The aluminium selenide was prepared by igniting, by means of magnesium ribbon, an intimate mixture of finely powdered aluminium (2·7 g.) and selenium (12 g.).

2-*Methylseleno*isochromanium *Iodide*.—An excess of methyl iodide was added to a methyl-alcoholic solution of the selenide, which was then refluxed until the *iodide* started to crystallise. The mixture was cooled, diluted with ether, and the iodide collected and recrystallised from methyl alcohol; colourless needles, m. p. 146° (efferv.) (Found: C, 35·4; H, 4·1. $C_{10}H_{13}ISe$ requires C, 35·4; H, 3·8%).

*Seleno*isochroman *Dichloride*.—When solutions of the selenide and of chlorine (in excess), each in cold carbon tetrachloride, were mixed, the *dichloride* was rapidly precipitated; when collected and recrystallised from alcohol, it formed colourless plates, m. p. 138° (decomp. to green liquid) (Found: C, 39·9; H, 3·9. $C_9H_{10}Cl_2Se$ requires C, 40·3; H, 3·7%).

The *dibromide*, similarly prepared by using a solution of bromine (1 mol.), recrystallised from alcohol as pale yellow needles, m. p. 149° (decomp. with preliminary darkening) (Found: Br, 44·4. $C_9H_{10}Br_2Se$ requires Br, 44·8%).

*Seleno*isochroman *Oxide* (III).—(*a*) A mixture of the powdered dibromide and an aqueous N-sodium hydroxide solution (2 equivs.) was shaken until clear, and then evaporated to dryness in a desiccator at room temperature. The residue was extracted with chloroform, and the filtered extract, similarly evaporated, deposited colourless crystals of the *oxide*, m. p. 104—105° (Found: C, 49·4; H, 5·09. $C_9H_{10}OSe$ requires C, 50·7; H, 4·7%). When this preparation was repeated on a larger scale, considerable decomposition occurred owing to the longer time required for the two evaporations, and the residue formed a viscous, semi-solid mass, from which the pure selenide was ultimately isolated.

(*b*) Silver oxide (1·7 g., 1·54 mols.) was added to a solution of the dibromide (1·7 g.) in hot water (40 c.c.), and the mixture then boiled for 10 minutes (charcoal); the filtrate, cooled and evaporated in a desiccator at room temperature, gave a crystalline residue of the crude oxide, which after recrystallisation from dioxan had m. p. 100—102° (Found: C, 50·0; H, 4·9%). The odour of the selenide was detected during the above boiling; evaporation of the aqueous filtrate at 30—40° gave much decomposition, and the residue remained liquid.

The selenoxide is freely soluble in water, methyl and ethyl alcohol, and in chloroform, less so in acetone, and almost insoluble in benzene and carbon tetrachloride. An aqueous solution, treated with concentrated hydrochloric acid, furnished the dichloride, m. p. 140° (efferv., mixed and unmixed). An alcoholic solution of the oxide, treated with alcoholic picric acid, gave a yellow precipitate which, after one and two recrystallisations from alcohol, had m. p. 97—103° and 120—123°, respectively, the latter value being unchanged by further crystallisation; analysis indicated that the final compound was the 2-*ethoxyseleno*isochromanium *picrate* (A) instead of the expected hydroxy-picrate (B) [Found: C, 43·8; H, 3·7; N, 9·1. $C_{17}H_{17}O_8N_3Se$ (A) requires C, 43·4; H, 3·6; N, 8·9%. $C_{15}H_{13}O_8N_3Se$ (B) requires C, 40·7; H, 2·9; N, 9·5%].

Action of Chloramine-T.—A solution of the selenide (0·749 g.) and anhydrous chloramine-T (0·862 g., 1 mol.) in alcohol (20 c.c.) was refluxed for 20 minutes, filtered to remove sodium chloride, and evaporated in a desiccator at room temperature. The semi-solid residue, when triturated with ether, furnished a white solid, which, after two recrystallisations from acetone, had m. p. 119° (efferv.) and was nitrogen-free; this compound was a particularly pure sample of the selenoxide, since its aqueous solution, treated with concentrated hydrochloride acid, deposited the dichloride, white crystals from alcohol, m. p. 140° (efferv., mixed and unmixed). The original ethereal washings furnished the selenide (identified as the methiodide), whereas the acetone mother-liquors afforded toluene-*p*-sulphonamide, white crystals from benzene, m. p. 133—135° (mixed and unmixed).

2-*Hydroxyseleno*isochromanium d-*Bromocamphorsulphonate*.—A solution of the selenoxide (III) in dilute hydrochloric acid (1 mol. of acid) was mixed with an aqueous solution of silver *d*-bromocamphorsulphonate (1 mol.), boiled for 5 minutes, filtered, and cooled. Colourless crystals of the *hydroxy*-d-*bromocamphorsulphonate*, m. p. 125—133° (decomp.), were deposited; α +1·20°, $[M]$ +292° (*c*, 0·539% in alcohol), the rotation being observed 20 minutes after contact of the solute and solvent; α +1·09°, $[M]$ +260° (*c*, 0·549% in chloroform). This salt was now recrystallised four times from ethyl acetate, from which it separated in hard crystals which apparently contained solvent of crystallisation, for they effloresced in a vacuum at room temperature; m. p. 117—123° (decomp.) (Found: C, 43·3; H, 5·1. $C_{19}H_{25}O_5BrSSe$ requires C, 43·5; H, 4·8%); α +1·12°, $[M]$ +266° (*c*, 0·551% in chloroform).

The ethyl acetate mother-liquors, when set aside for several days, deposited fine needles which were entirely different in appearance from those above, and did not effloresce in a vacuum; m. p. 114—118° (Found: C, 42·6; H, 5·2%). A 0·563% chloroform solution had, however, α +1·13°, $[M]$ +263°.

The pure bromocamphorsulphonate slowly decomposed to a brown liquid when kept at room temperature even in the dark; this decomposition was much slower than that of the selenoxide.

dl-2-p-*Chlorophenacylseleno*isochromanium *Bromide*.—*p*-Chlorophenacyl bromide (8·2 g.) was added to a solution of the selenide (7·3 g., 1 mol.) in hot alcohol (50 c.c.), and the solution refluxed for 5 minutes and then cooled. After the semi-solid product had been diluted with benzene (*ca.* 20 c.c.), the *bromide* was collected, washed with alcohol and benzene, and recrystallised from alcohol; colourless crystals (12·2 g.), m. p. 122° (Found: C, 47·8; H, 3·55. $C_{17}H_{16}OClBrSe$ requires C, 47·4; H, 3·7%). The dl-*picrate* was readily obtained when alcoholic picric acid was added to a boiling alcoholic solution of the bromide; yellow crystals from alcoholic acetone, m. p. 167—168° (Found: N, 7·4. $C_{23}H_{16}O_8N_3ClSe$ requires N, 7·3%).

Resolution of the 2-p-*Chlorophenacylseleno*isochromanium *Ion*.—Solutions of the above bromide (12·7 g.) and of silver

d-bromocamphorsulphonate (14·2 g., 1 mol.), each in hot 90% alcohol (200 c.c.), were mixed, boiled for a short period, and filtered. The filtrate, when set aside, deposited the optically impure crystalline *selenoisochromanium* d-*bromocamphorsulphonate*, m. p. 155—157°. This was recrystallised seven times from alcohol, the consecutive crops having these rotations in alcoholic solution:

G. solute/100 c.c. solvent	0·613	0·720	0·447	0·363	0·390	0·343	0·341
α	−0·45°	−0·88°	−0·64°	−0·56°	−0·65°	−0·57°	−0·56°
$[M]$	− 120	− 202	− 236	− 254	− 275	− 275	− 271

The final crop was therefore the optically pure *l*-selenonium *d*-sulphonate; m. p. 157—159° with preliminary softening (Found: C, 48·8; H, 4·6. $C_{27}H_{30}O_5ClBrSSe$ requires C, 49·1; H, 4·5%). This salt is considerably more soluble in methyl alcohol, in which a 0·681% solution had α −1·21°, $[M]$ −293°. No change in rotation of solutions in either solvent at room temperature could be detected over 24 hours. A 1·976% solution in methyl alcohol was refluxed for 1 hour and cooled; the solution, diluted to 0·659%, had α −0·85°, $[M]$ −213°. The rotations of the ions being assumed to be additive, this indicates that the racemisation of the selenonium ion had progressed by *ca.* 14%.

1-2-p-*Chlorophenacylselenoisochromanium Picrate*.—A saturated methyl-alcoholic picric acid solution (10 c.c.) was added with stirring to a solution of the above optically pure *l*-selenonium *d*-sulphonate (0·8 g.) in methyl alcohol (30 c.c.) previously cooled to 0°. The precipitated l-*selenonium picrate* was collected, washed with alcohol and water, and dried, a further crop being obtained by cautious dilution of the original filtrate with water; the united crops (0·6 g.) had m. p. 174—175° (Found: C, 47·4; H, 3·4; N, 7·6. $C_{23}H_{18}O_9N_3ClSe$ requires C, 47·7; H, 3·1; N, 7·3%); α −0·80°, $[M]$ −531° (*c*, 0·218% in acetone). The preparation was repeated but with sodium picrate; the united crops had α −1·55°, $[M]$, −533° (*c*, 0·421% in acetone).

A portion of this *l*-picrate was recrystallised from methyl alcohol; its m. p. was unchanged, and a 0·396% acetone solution had α −1·43°, $[M]$ −522°. A 0·409% solution of the *l*-picrate, in acetone containing 2% of water, had α −1·41°, $[M]$ −499°. None of the above solutions showed any change in rotation at room temperature during 48 hours; although the presence of water in the acetone causes a fall in rotation, this is evidently at room temperature a solvent effect and is not due to partial racemisation.

In the following experiments to determine the degree of optical stability of the *l*-picrate in dry and in aqueous acetone, and in methyl alcohol, the picrate used in (*a*) and (*b*) had initially $[M]$ −531°, that in (*c*) $[M]$ −499°, and that in (*d*) $[M]$ −522°. (*a*) A solution of the picrate (0·0988 g.) in acetone (10 c.c.) was heated under reflux for 30 minutes, cooled, and diluted to 30 c.c. (*i.e.*, 0·329%). It then had α −1·18°, $[M]$, −518°, racemisation having therefore proceeded by *ca.* 2·4%. (*b*) Experiment (*a*) was repeated, but with 7·5 hours' refluxing and 0·1307 g. of picrate. The diluted solution (0·436%) had α −1·41°, $[M]$ −465°, racemisation having proceeded by *ca.* 16%. (*c*) A solution of the picrate (0·1530 g.) in acetone (10 c.c.) and water (0·5 c.c.) was refluxed for 1 hour. After dilution with acetone as before, the solution (0·510%) had α −1·69°, $[M]$ −479°; racemisation, *ca.* 4%. (*d*) A 1·00% solution in methyl alcohol was refluxed for 1 hour, cooled, and evaporated to dryness in a desiccator at room temperature; a 0·357% acetone solution of the residue had α −1·21°, $[M]$ −491°; racemisation, *ca.* 5%.

In a preliminary note (*Nature*, 1943, **152**, 750) it was stated that refluxing of an acetone solution of this picrate for 1·25 hours caused complete racemisation; this statement is misleading, as it was subsequently found that this rapid racemisation was due to an unsuspectedly high proportion of water in the particular acetone used.

The inactive bromide was now treated as before but with silver *l*-bromocamphorsulphonate. Nine recrystallisations of the product from alcohol gave the optically pure d-*selenoisochromanium* l-*bromocamphorsulphonate*, unchanged by further recrystallisations; m. p. 158—160° (Found: C, 49·0; H, 4·8%); α +0·56°, $[M]$ +276° (*c*, 0·332% in alcohol).

d-2-p-*Chlorophenacylselenoisochromanium Picrate*.—This was isolated precisely as the *l*-picrate. A 0·347% acetone solution of the dried but unrecrystallised salt had α +1·21°, $[M]$ +504°; after recrystallisation from methyl alcohol, this d-*picrate* had m. p. 170—171·5° (Found: C, 47·85; H, 3·5; N, 7·3%), α +1·50°, $[M]$ +504° (*c*, 0·430% in acetone). Several preparations of this picrate had rotations closely approaching this value. The difference between the values obtained for the rotations of the *l*- and the *d*-picrate is, however, difficult to explain.

The l-*Selenoisochromanium Mercuritri-iodide*.—Two solutions in methyl alcohol were prepared, one containing the *l*-selenonium *d*-bromocamphorsulphonate (1 mol.) and the other both potassium iodide (1 mol.) and mercuric iodide (1 mol.). These were cooled to 0° and rapidly mixed; the l-*mercuritri-iodide* separated as a pale yellow microcrystalline powder, m. p. 65—100° (decomp.) (Crop I), which was collected, washed with methyl alcohol, and dried. Cautious dilution of the original mother-liquor with water gave an emulsion, which ultimately deposited a yellow crystalline powder of unchanged m. p. (Crop II). A 0·273% acetone solution of Crop I at 16° gave the following rotations after the stated period from initial preparation of the solution:

Time (hrs.).	α_{5780}.	$[M]_{5780}$.	α_{5461}.	$[M]_{5461}$.	$\alpha_{5780}/\alpha_{5461}$.
1·5	−0·56°	−478°	−0·65°	−554°	0·863
18·5	−0·55	−469	−0·61	−520	0·902
65	−0·49	−418	−0·54	−460	0·909

A 0·292% acetone solution of Crop II at 16° had α_{5780} −0·67°, $[M]_{5780}$ −535°, α_{5461} −0·74°, $[M]_{5461}$ −591°; $\alpha_{5780}/\alpha_{5461}$ 0·905.

To investigate this mutarotation more fully, this preparation was repeated on a larger scale; analysis showed that only Crop II was the chemically pure mercuritri-iodide (Found: Crop I, C, 23·25; H, 2·2. Crop II, C, 21·6; H, 2·0. $C_{17}H_{16}OClI_2HgSe$ requires C, 21·9; H, 1·7%), although the cations in the two crops were undoubtedly chemically identical. The mutarotation of Crop II was slower than that of Crop I, but was not appreciably affected by the concentration; the initial rotations of both crops were smaller than those obtained in the earlier experiment, owing to the longer time required to isolate the larger crops.

The following table shows the rotations after specified times of (A) a 0·674% solution of Crop I; (B) a 0·671% solution of Crop II; (C) a 0·271% solution of Crop II, all in acetone at 18°.

Time.	α_{5893}.	$[M]_{5893}$.	α_{5780}.	$[M]_{5780}$.	α_{5461}.	$[M]_{5461}$.
(A) 35—60 Mins.	−0·86°	−297°	−0·91°	−315°	−1·07°	−370°
1 Day	−0·79	−273	−0·87	−301	−1·01	−349
9 Days	−0·33	−114	−0·40	−138	−0·46	−159
(B) 35—60 Mins.	−1·04	−361	−1·17	−406	−1·37	−476
9 Days	−0·99	−344	−1·07	−372	−1·28	−444
(C) 35—50 Mins.	−0·44	−378	−0·49	−421	−0·56	−481
9 Days	−0·37	−318	−0·41	−352	−0·50	−430

Many attempts were made to convert the *l*-selenonium *d*-bromocamphorsulphonate into a salt having an inactive colourless cation (*i.e.*, without absorption in the visible spectrum), so that the rotatory dispersion and the absorption spectrum could be correlated. Difficulties due primarily to comparative solubilities nullified all such attempts.

Telluroisochroman.—An aqueous solution of sodium telluride was prepared (cf. Balfe, Chaplin, and Phillips, J., 1938, 344) by adding rongalite (34 g.) to a solution of sodium hydroxide (26 g.) in water (100 c.c.) contained in a flask fitted with a reflux water-condenser and an inlet tube, by which the air was replaced by a stream of coal-gas; finely divided tellurium (15 g., precipitated by sulphur dioxide reduction of a solution of the dioxide in hydrochloric acid) was added, and the mixture heated on a water-bath for 30 minutes with frequent shaking, a permanganate-coloured solution being thus obtained. Alcohol (100 c.c.) was now added, followed by a solution of *o*-β-bromoethylbenzyl bromide (25 g.) in hot alcohol (150 c.c.), and the mixture, which formed two layers, was then heated for a further 2 hours with occasional vigorous shaking. The alcohol was now distilled off, the stream of coal-gas having been maintained throughout the preparation until the distillation was complete.

The residue was cooled, broken up, and shaken vigorously with a mixture of water (300 c.c.) and ether (300 c.c.), the undissolved residue being then filtered off. The ethereal extract was separated, washed with water, dried (sodium sulphate), and distilled, the *telluroisochroman* being collected as a pale yellow liquid (8·5 g., 37%), b. p. 116—126°/0·3 mm., which readily crystallised on cooling. A second crop (3·8 g.) was obtained when the undissolved residue was extracted with hot alcohol (50 c.c.), and the extract filtered and cooled. The united crops were recrystallised from methyl alcohol, the solution being cooled in an atmosphere of carbon dioxide; silky needles, m. p. 63·5—64° (Found: C, 44·1; H, 4·1; *M*, ebullioscopic in 0·860% alcoholic solution, 244. $C_9H_{10}Te$ requires C, 43·9; H, 4·1%; *M*, 246).

2-Methyltelluroisochromanium Iodide.—The telluride rapidly dissolved when added to an excess of cold methyl iodide, and the yellow solution readily deposited the crystalline *iodide*, which, after addition of alcohol to complete the precipitation, was collected and recrystallised from 50% aqueous methyl alcohol, from which it separated as a *monomethyl-alcoholate*, m. p. 260° (efferv.) in a sealed tube (Found: C, 31·7; H, 3·8. $C_{10}H_{13}ITe,CH_4O$ requires C, 31·4; H, 4·05%). The iodide is almost insoluble in boiling ethyl alcohol.

Telluroisochroman Dibromide.—When a solution of bromine (1 mol.) in carbon tetrachloride was added to one of the telluride in chloroform, rapid addition occurred, followed by separation of the *dibromide*, which, twice recrystallised from alcohol, furnished colourless crystals, m. p. 166—167° (Found: C, 26·8; H, 2·8. $C_9H_{10}Br_2Te$ requires C, 26·6; H, 2·5%).

Action of Hydrogen Peroxide on the Telluride.—Aqueous hydrogen peroxide ("20-vol.") was added dropwise to a boiling alcoholic solution of the telluride until no further precipitate was obtained. The white amorphous product was collected, thoroughly washed in turn with alcohol, water and alcohol again, and dried. It then darkened and shrunk when heated to 180° but did not melt below 270°; it was insoluble in all the usual organic solvents except chloroform, and could not be recrystallised. These properties are closely similar to those of the oxidation products of other tellurides described by Balfe, Chaplin, and Phillips (*loc. cit.*). The composition of the compound indicated that the oxidation had proceeded beyond the tellurone stage, without, however, complete conversion into the "hydroxy-perhydrate" stage, of type $a_2Te(OH)\cdot O\cdot OH$, described by these authors (Found: C, 37·8; H, 4·1. Calc. for $C_9H_{10}O_3Te$: C, 38·9; H, 3·6%. $C_9H_{12}O_3Te$ requires C, 36·6; H, 4·1%).

dl-2-p-*Chlorophenacyltelluroisochromanium Bromide.*—When *p*-chlorophenacyl bromide (1 mol.) was added to a solution of the telluride in boiling alcohol, the *bromide* was rapidly precipitated; after 5 minutes' boiling, it was collected from the hot solution, washed with alcohol, and recrystallised from methyl alcohol; m. p. 161—163° with preliminary softening (Found: C, 42·8; H, 3·6. $C_{17}H_{16}OClBrTe$ requires C, 42·5; H, 3·3%). The bromide is only slightly soluble in boiling ethyl alcohol, but moderately soluble in boiling methyl alcohol.

This preparation was successfully repeated on several occasions; on one occasion, however, the boiling alcoholic solution remained clear, but on cooling deposited *telluroisochroman hydroxybromide*, m. p. 145° after two recrystallisations from alcohol (Found: C, 31·1; H, 3·0. $C_9H_{11}OBrTe$ requires C, 31·3; H, 3·2%); its identity was confirmed by the addition of aqueous hydrobromic acid to its hot alcoholic solution, whereby on cooling long colourless needles of the dibromide were deposited, m. p. 166—167° alone and when mixed with an authentic sample (Found: C, 26·9; H, 2·3%). That this result was due to the presence of water in the alcohol was demonstrated by the following experiment. A mixture of the bromide (1 g.), alcohol (20 c.c.), and water (0·5 c.c.) was refluxed for 45 minutes. The solution, which had rapidly become clear, was then cooled and evaporated to dryness in a vacuum at room temperature. The glassy residue, when triturated with ether, readily gave a crystalline residue which was collected. The ethereal filtrate contained *p*-chloroacetophenone, detected by its odour and by conversion into the semicarbazone, m. p. 204—206° (Found: C, 52·2; H, 5·5; N, 19·8. Calc. for $C_9H_{10}ON_3Cl$: C, 51·1; H, 4·7; N, 19·9%). The crystalline residue had m. p. 80—120°, raised to 140—168° by recrystallisation from alcohol; it was evidently the impure telluride hydroxybromide, since treatment with hydrobromic acid (as above) furnished the crystalline dibromide, m. p. 165—165·5°, alone and mixed with an authentic sample (Found: C, 27·15; H, 2·7%).

dl-2-p-*Chlorophenacyltelluroisochromanium Picrate.*—This was immediately precipitated when hot methyl-alcoholic solutions of the bromide and of sodium picrate were mixed; yellow crystals, m. p. 198—199° (decomp.) after recrystallisation from acetone (Found: C, 44·5; H, 3·3; N, 6·6. $C_{23}H_{18}O_8N_3ClTe$ requires C, 44·0; H, 2·9; N, 6·7%); it is almost insoluble in hot methyl and ethyl alcohol, and only slightly soluble in hot acetone.

Partial Resolution of the 2-p-*Chlorophenacyltelluroisochromanium Ion.*—(A). *The* l-*ion.* (1) Solutions of the telluronium bromide (2 g.) and of silver *d*-bromocamphorsulphonate (2 g., 1 mol.), each in boiling methyl alcohol (100 c.c. and 50 c.c.), were mixed, boiled for 2 minutes, filtered, and the filtrate evaporated in a vacuum desiccator. The partly crystalline residue, which had an odour resembling that of an aryl alkyl ketone, was triturated with cold alcohol (10 c.c.), and the insoluble white crystalline salt collected, and washed with alcohol and ether; m. p. 143—154°; 1 g. Recrystallisation from ethyl alcohol furnished the chemically pure but optically impure l-*telluronium* d-*bromocamphorsulphonate*, colourless needles, m. p. 147—158° (Found: C, 45·7; H, 4·6. $C_{27}H_{39}O_4ClBrSTe$ requires C, 45·7; H, 4·3%), α −0·55°, [*M*] −99° (*c*, 0·987% in methyl alcohol). This solution showed the following mutarotation at 15°:

Time, hrs.	α.	[*M*].	Time, hrs.	α.	[*M*].	Time, hrs.	α.	[*M*].
2	−0·26°	− 47°	26	+0·67°	+120°	95	+1·44°	+259°
4	−0·12	− 21·5	29	+0·75	+135	120	+1·52	+273
6	−0·02	− 3	32	+0·805	+145	143	+1·575	+282
8	+0·10	+ 18	47	+1·05	+188	168	+1·61	+289
23	+0·62	+110	56	+1·155	+207	215	+1·65	+296

(2) The above preparation was repeated upon quadruple quantities. The less soluble fraction of the sulphonate, after being extracted with cold alcohol but not recrystallised, had $\alpha^{16°}$ −0·45°, [*M*] −81° (*c*, 1·007% in methyl alcohol); these readings were taken 10 minutes after wetting the salt with the solvent, and after 18 hours had changed to $\alpha^{16°}$ +0·48°, [*M*] +85°. Another portion of this salt (0·2170 g.) was refluxed with methyl alcohol (10 c.c.) for 1 hour: the solution was cooled, diluted to 30 c.c. (*i.e.*, 0·723% solution), and then had α +0·95°, [*M*] +233°.

(3) In another similar preparation, the extracted but unrecrystallised sulphonate had $\alpha^{16°}$ +0·15°, [*M*] +38° (*c*, 0·705% in methyl alcohol) within 15 minutes of dissolution. A portion of this salt was recrystallised from benzene, and then had $\alpha^{16°}$ +0·11°, [*M*] +28° (*c*, 0·702% in methyl alcohol). A second portion was rapidly recrystallised from ethyl alcohol, and was then chemically pure (Found : C, 45·8; H, 4·3%), m. p. 145—152°; the mutarotation of a 0·987% methyl-alcoholic solution of this recrystallised sample is given on p. 39.

(B). *The* d-*ion*. (1) The cold ethyl-alcoholic extract obtained in Experiment (A, 1) was evaporated in a vacuum desiccator, and the optically impure *d*-telluronium *d*-bromocamphorsulphonate obtained as a friable glass, $\alpha^{15°}$ +2·79°, [*M*] +498° (*c*, 0·393% in methyl alcohol), and gave the following values during mutarotation :

Time (hours)	3	19	27	67	91	115	139	187	235
$\alpha^{15°}$	+2·72°	+2·49°	+2·38°	+2·02°	+1·91°	+1·86°	+1·80°	+1·79°	+1·75°
$[M]^{15°}$	486	445	425	361	341	332	321	320	312

(2) In another similar preparation, the friable glass thus obtained was thoroughly triturated with petrol (b. p. 40—60°); the residual hygroscopic salt, m. p. 55—70°, had $\alpha^{16°}$ +1·74°, [*M*] +579° 15 mins. after preparation and $\alpha^{16°}$ +1·59°, [*M*] +529° 19 hrs. after (*c*, 0·533% in methyl alcohol).

The l-*Telluronium Picrate*.—When a methyl-alcoholic solution of picric acid was added to a solution of the *l*-telluronium *d*-bromocamphorsulphonate (2 g., having [*M*] −81° in methyl alcohol) in cold methyl alcohol (200 c.c.), the optically impure l-*picrate* was immediately precipitated. It was collected, washed with methyl alcohol, and dried (Found : C, 44·1; H, 3·0; N, 6·6. $C_{23}H_{18}O_8N_3ClTe$ requires C, 44·0; H, 2·9; N, 6·7%); m. p. 192—193° (decomp.), α −0·37°, [*M*] −280° (*c*, 0·207% in acetone). Cautious addition of water to the original mother-liquor precipitated a much more active sample of the picrate, $\alpha^{14°}$ −1·34°, [*M*] −600° (*c*, 0·350% in acetone).

The fact that the latter sample was appreciably more soluble in acetone than the former enabled optical purification to be taken further. The former sample, [*M*] −280°, was vigorously shaken with acetone (30 c.c./1 g. of picrate), and the mixture then filtered; the undissolved residue had [*M*] −77° (*c*, 0·183% in acetone). The filtrate, evaporated to dryness at room temperature, deposited the chemically pure picrate (Found : C, 44·5; H, 2·9%), m. p. 187° (decomp.), $\alpha^{14°}$ −1·38°, [*M*] −632° (*c*, 0·342% in acetone).

A 0·418% solution of this picrate in acetone which contained 0·4% of water underwent very slow racemisation : since the solution was not thermostatically controlled, its temperature at each reading is given :

Days.	Temp.	α.	[*M*].	$k \times 10^4$.	Days.	Temp.	α.	[*M*].	$k \times 10^4$.
—	13·5°	−1·68°	−630°	—	10	16°	−0·35°	−131°	28
1	13·5	−1·455	−546	26	12	17	−0·22	− 82·5	30·5
3	13	−1·155	−433	23	14	17	−0·12	− 45	34
5	14	−0·90	−340	23	17	16·5	−0·06	− 22·5	35
7	14	−0·65	−240	25	19	16	−0·03	− 11	38
8·5	15	−0·48	−180	28	21	16	0	0	—

After racemisation was complete, the solvent was removed in a vacuum at room temperature; the residue had a pronounced odour of an aromatic ketone, but when washed with ether it furnished the chemically pure picrate (Found : C, 43·7; H, 3·2; N, 7·0%).

Another solution of the above picrate (having [*M*] −632°) in acetone containing *ca.* 2% of water showed much more rapid racemisation. For this purpose, the picrate (0·1142 g.) was dissolved in acetone, water (0·5 c.c.) added, and the solution made up to 30 c.c. with acetone, giving a 0·347% solution. This furnished the following readings :

Hours.	Temp.	α.	[*M*].	$k \times 10^3$.	Hours.	Temp.	α.	[*M*].	$k \times 10^3$.
—	14°	−1·36°	−560°	—	27	14°	−0·44°	−180°	18
2	14	−1·11	−457	44	42	14	−0·31	−130	15
3	14	−1·02	−420	42	66	15	−0·18	−74	13
4	14	−0·96	−395	38	90	15	−0·08	−33	14
6	14	−0·87	−360	31	114	16	−0·03	−12	14·5
18	14	−0·59	−240	20	139	16	0	0	—

Removal of the solvent as before again gave a residue having an odour of a ketone; recrystallisation from aqueous alcohol gave a product, m. p. 195° (decomp. with preliminary darkening), whose composition suggests a *monohydrate* of the picrate (Found : C, 42·8; H, 3·35. $C_{23}H_{18}O_8N_3ClTe,H_2O$ requires C, 42·8; H, 3·1%).

A higher value for the rotation of the picrate was obtained by the following experiment. A saturated acetone solution of the *dl*-picrate was found (by direct evaporation in a vacuum at room temperature) to contain 0·068 g. of picrate/30 c.c. This volume of an acetone solution, saturated with respect to both the *l*- and the *dl*-picrate, was found by similar treatment to contain 0·396 g. of the mixed product, which in 0·352% acetone solution had $\alpha^{15·5°}$ −1·40°, [*M*] −624°; subtraction of the above weight of the *dl*-picrate shows that the *l*-picrate had [*M*] −753°. This estimation ignores the mutual influence of the picrates on their solubilities, and also the racemisation that must have occurred during the second slow evaporation. The optically pure picrate has undoubtedly an even higher rotation than that calculated.

The d-*Telluronium Picrate*.—The more soluble, optically impure, *d*-telluronium *d*-bromocamphorsulphonate, having [*M*] +579°, was treated in methyl-alcoholic solution with sodium picrate (as already described) to precipitate the d-*picrate*, and a second crop obtained by dilution of the filtrate with water. A 0·178% acetone solution of the first crop had $\alpha^{15·5°}$ +0·42°, [*M*] +370°, and a 0·190% solution of the second crop had $\alpha^{15·5°}$ +0·19°, [*M*] +206°. These crops were united and extracted with cold acetone (30 c.c./g.); the undissolved material was filtered off, and the filtrate on evaporation gave the *d*-picrate, $\alpha^{15·5°}$ +1·28°, [*M*] +578° (*c*, 0·347% in acetone). This was again extracted with insufficient cold acetone for complete dissolution, and the filtrate on evaporation gave a further sample of the *d*-picrate, which had $\alpha^{15·5°}$ +1·27°, [*M*] +575° (*c*, 0·347% in acetone); this sample had m. p. 189° (decomp.) and was chemically pure (Found : C, 44·1; H, 3·3; N, 6·95%), but still optically impure.

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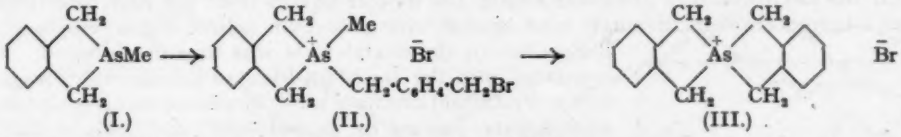
14. *The Synthetic Application of o-β-Bromoethylbenzyl Bromide. Part VI. The Preparation and Optical Resolution of a Spirocyclic Arsonium Salt possessing Molecular Dissymmetry.*

By Frederick G. Holliman and Frederick G. Mann.

2-Methyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline unites with *o*-β-bromoethylbenzyl bromide to give a quaternary salt which on heating loses methyl bromide, forming the highly crystalline As-spiro-*bis*-1 : 2 : 3 : 4-*tetrahydroisoarsinolinium bromide* (VI). The arsenic atom in this compound is symmetric, but the disposition of the ring systems around this tetrahedral atom causes the compound to possess molecular dissymmetry. It has therefore been resolved *via* the bromocamphorsulphonates, and the d- and l-*iodides* isolated having $[M]_D$ + 342° and − 344° in chloroform solution. The stability of the heterocyclic rings gives the compound high optical stability, and the rotation of the iodide remains unchanged in chloroform at 18° for four weeks.

The only other known optically stable arsonium salt is 2-phenyl-2-*p*-chlorophenacyl-1 : 2 : 3 : 4-tetrahydro-*iso*arsinolinium iodide, which contains an asymmetric arsenic atom (Holliman and Mann, J., 1943, 550).

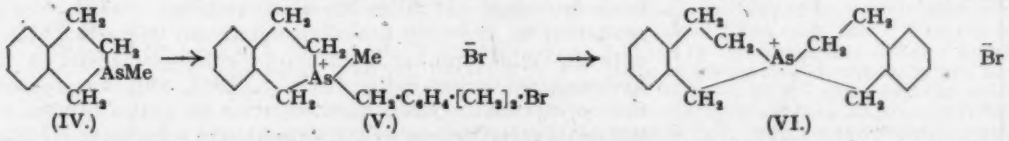
It has recently been shown by Lyon and Mann (this vol., p. 30) that 2-methyl*iso*arsindoline (I) readily combines with one equivalent of *o*-xylylene dibromide to form 2-*o*-(bromomethyl)benzyl-2-methyl*iso*arsindolinium bromide (II), which on heating loses methyl bromide with the formation of the highly crystalline *As-spiro*-bis*iso*arsindolinium bromide (III). It appeared probable that this novel method for the synthesis of spirocyclic arsonium salts could be applied to other heterocyclic arsines, provided the ring system in the latter



(I.) (II.) (III.)

possessed sufficient stability to remain unchanged throughout the necessary reactions; moreover, our earlier work on the tetrahydro*iso*arsinolines (Holliman and Mann, J., 1943, 547) offered a promising means whereby dissymmetric arsonium salts might be obtained by the above series of reactions.

Accordingly, we have treated 2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline (IV) with one molecular equivalent of *o*-β-bromoethylbenzyl bromide; union occurred readily, but the arsonium bromide formed a viscous glass and purification was not attempted. Its constitution is uncertain, but since the bromomethyl group in *o*-β-bromoethylbenzyl bromide is undoubtedly more reactive than the β-bromoethyl group, this intermediate arsonium salt has probably the structure (V). When this glassy product was heated at 14 mm. pressure, it formed a mobile liquid which underwent marked effervescence as the temperature rose above 100°, and ultimately, after one hour's heating at 200°, it crystallised even at this elevated temperature. The cold product,

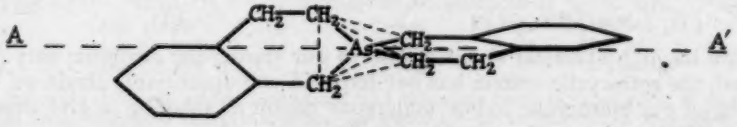


(IV.) (V.) (VI.)

after recrystallisation from water or alcohol (each containing a small quantity of hydrobromic acid), furnished the crystalline As-spiro-*bis*-1 : 2 : 3 : 4-*tetrahydroisoarsinolinium bromide* (VI), m. p. 288—290°, in 38% yield. There were indications that other reactions also occurred during the thermal decomposition, but the by-products were not investigated.

The arsonium bromide (VI) has very considerable stereochemical interest. Physical evidence shows that the 4-covalent arsenic atom has the tetrahedral configuration (Mann, Purdie, and Wells, J., 1936, 1503; 1937, 1828; Mann and Wells, J., 1938, 702), although there is no decisive chemical evidence on this point. If this configuration applies also to the arsonium bromide (VI), it follows that, although the arsenic atom in this compound is not asymmetric, the salt itself, by virtue of the disposition of the ring systems, should possess molecular dissymmetry and therefore be susceptible to optical resolution. The configuration of the arsonium ion is shown in (VIA), where an axis $A \cdots A'$ of the tetrahedral arsenic atom has been inserted to emphasise the dissymmetry of the arsonium ion.

The arsonium bromide (VI) was therefore converted into the d-*bromocamphorsulphonate*; this was initially obtained as a viscous syrup which could not be recrystallised from organic solvents, but readily separated



(VIA.)

from a warm aqueous solution as colourless crystals, having m. p. 70—74°, and $[M]_D$ + 202° in alcoholic solution. Fractional recrystallisation from water now caused the m. p. to rise and the rotation to fall; after

five recrystallisations these values became constant, and the optically pure *l*-arsonium *d*-bromocamphorsulphonate was thus obtained, m. p. 186—187°, $[M]_D$ + 119° in alcoholic solution.

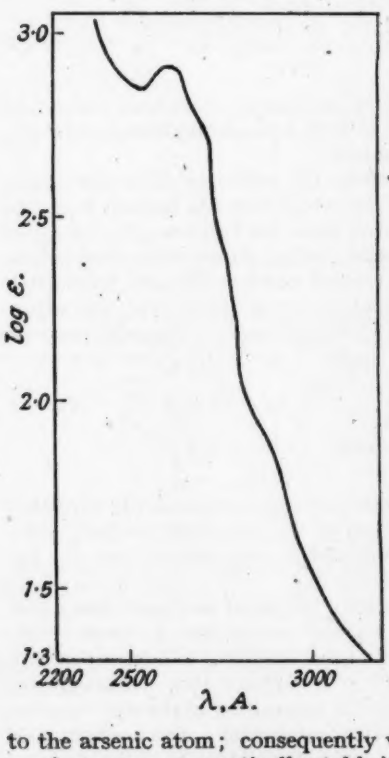
Treatment of the above *d*-bromocamphorsulphonate with sodium iodide in alcoholic solution furnished long, colourless needles of the optically pure l-As-spiro-*bis*-1 : 2 : 3 : 4-*tetrahydroisoarsinolinium iodide* (as VI), having m. p. 226—228° and $[M]_D$ − 344° in chloroform solution. The rotation of this compound was unaffected by recrystallisation from hot alcohol, and that of a solution in chloroform remained unchanged during four weeks at 18° when protected from light: the iodide has therefore very considerable optical activity.

The following values for the rotatory dispersion in the visible spectrum have been obtained for a 0·385% solution of the *l*-iodide in chloroform. The calculated rotations are based on the equation $\alpha = k/(\lambda^2 - \lambda_0^2)$, where the rotation constant $k = 0{\cdot}3547$ and $\lambda_0^2 = 0{\cdot}0536$. The close agreement between the observed and the calculated rotations shows that the iodide possesses simple rotatory dispersion. From this equation, the dispersion constant $\lambda_0 = 2316$ A.

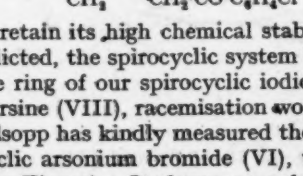
Source of light.	Li.	Li.	Na.	Hg.	Hg.	Cu.*	Cu.*	Zn.*	Hg.
λ, A.	6708	6104	5893	5780	5461	5219	5105	4811	4358
α, obs.	−0·90°	−1·09°	−1·21°	−1·27°	−1·45°	−1·60°	−1·71°	−2·02°	−2·60°
[M]	−256	−310	−344	−363	−413	−455	−487	−575	−740
α, calc.	−0·89	−1·11	−1·21	−1·26	−1·45	−1·62	−1·71	−2·00	−2·60
α, obs.—α, calc.	+0·01	−0·02	0·00	+0·01	0·00	−0·02	0·00	+0·02	0·00

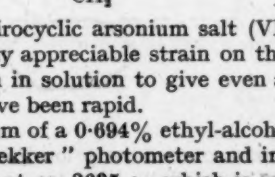
* Obtained from brass arc.

To obtain the dextrorotatory arsonium iodide, the mother-liquors from the first three recrystallisations of the above *d*-bromocamphorsulphonate were treated with potassium iodide, and a sample of the arsonium iodide rich in the dextro-form was thus precipitated. This was then converted into the arsonium *l*-bromo camphorsulphonate, which after four recrystallisations from water furnished the optically pure *d*-arsonium *l*-sulphonate, having m. p. 186—187° and $[M]_D$ − 123° in alcoholic solution. This in turn gave the pure d-As-spiro-*bis*-1 : 2 : 3 : 4-*tetrahydroisoarsinolinium iodide*, m. p. 225—228°, $[M]_D$ + 342° in chloroform solution.



The noteworthy feature of our new spirocyclic arsonium salts is their high optical stability, which is vividly shown by the fact that the activity of the bromocamphorsulphonates can withstand boiling water, whilst that of the iodides remains unchanged in chloroform, a solvent noted for its ready racemisation of optically active quaternary ammonium iodides (Pope and Harvey, J., 1901, **79**, 831; Jones *et al.*, J., 1904, **85**, 228; 1906, **89**, 285; 1908, **93**, 300). This optical stability must be in turn dependent on high chemical stability. When discussing the resolution of the only other arsonium salt hitherto obtained in an optically stable form, *viz.*, 2-phenyl-2-*p*-chlorophenacyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinolinium iodide (VII) (J., 1943, 550), we pointed out that the only probable mechanism whereby an optically active arsonium salt could racemise was by the formation in solution of a "dissociation-equilibrium" of the type $[abcdAs]X \rightleftarrows abcAs + dX$, originally suggested by Burrows and Turner (J., 1921, **119**, 426). Arsonium salts whose resolution had been attempted by earlier workers had possessed at least one alkyl group joined to the arsenic atom, and consequently the above "dissociation-equilibrium" was readily attained; hence the optical activity, if detected at all, was small and fleeting. In our salt (VII), we had evidence that the heterocyclic ring possessed great stability and that, in addition, the presence of the *p*-chlorine atom in the phenacyl radical appeared to strengthen the linkage of this radical to the arsenic atom; consequently very little (if any) dissociation to a tertiary arsine occurred, and the salt was in consequence optically stable in solution. It is evident that the heterocyclic ring in the phenylarsonium

(VII.) 



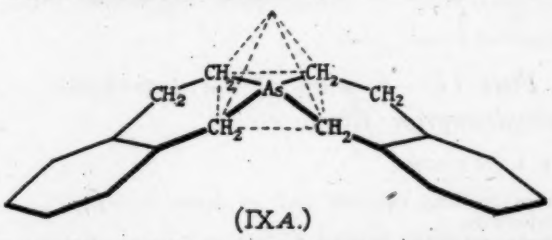
(VIII.)

salt (VII) must retain its high chemical stability also in our spirocyclic arsonium salt (VI) and that, as we confidently predicted, the spirocyclic system has not imposed any appreciable strain on the two heterocyclic rings. Had one ring of our spirocyclic iodide undergone fission in solution to give even a small proportion of the tertiary arsine (VIII), racemisation would undoubtedly have been rapid.

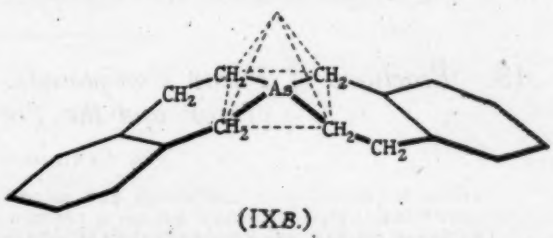
Dr. C. B. Allsopp has kindly measured the absorption spectrum of a 0·694% ethyl-alcoholic solution of the racemic spirocyclic arsonium bromide (VI), using a Hilger "Spekker" photometer and intermediate quartz spectrograph (see Figure). It shows a marked absorption band at *ca.* 2635 A., which is undoubtedly due to

ne two phenylene groups, but is otherwise without notable features over the range of wave-lengths used. he absorption spectrum of the *p*-chlorophenacyl arsonium iodide (VII) also showed this band, but showed addition a more intense band at 3115 A., due apparently to the *p*-chlorophenacyl radical. The two arsonium alts have similar dispersion constants [λ_0 = 2316 A. for (VI) and 2443 A. for (VII)], suggesting that in both ompounds the optical activity originates mainly in electronic transitions which are centred at the arsenic tom and correspond to absorption in this region; this cannot be determined decisively, however, without xtending the rotatory dispersion to much shorter wave-lengths. It is noteworthy that the two salts have lso closely similar rotations; *e.g.*, the *l*-arsonium iodide (VII) in 0·508% chloroform solution had $[M]_D$ − 352°, nd this close proximity of the two rotatory powers is maintained throughout the visible spectrum (cf. Holliman nd Mann, *loc. cit.*, p. 554).

Although the spirocyclic arsonium salt (VI) has some structural resemblance to the 4-phenyl-4′-carbethoxy-ispiperidinium-1 : 1′-spiran bromide resolved by Mills and Warren (J., 1925, **127**, 2507), it should be emphasised that the resolution of our arsonium salt confirms, but does not prove, the tetrahedral configuration of the 4-covalent arsenic atom. Mills and Warren's spirocyclic ammonium salt could have shown optical activity only if the 4-covalent nitrogen atom possessed a tetrahedral configuration : had this atom possessed the Bischoff pyramidal configuration, the salt could have existed in *cis*- and *trans*-isomerides, neither of which could have shown optical activity. If the 4-covalent arsenic atom possessed this pyramidal configuration, our



(IX*A*.)



(IX*B*.)

spirocyclic salt (VI) could also exist in geometric isomers, but of these only the *cis*-form (IXA) has a plane of symmetry, and the *trans*-form (IXB), having no element of symmetry, could show optical activity. None of the salts containing our spirocyclic arsonium ion showed, however, any evidence of existing in two geometric isomers.

Experimental.

All rotations were measured in a 4-dm. tube at 18°, the source of light (unless otherwise stated) being the sodium-D line, λ 5893.

dl-As-spiro-*Bis*-1 : 2 : 3 : 4-*tetrahydroisoarsinolinium Bromide* (VI).—A mixture of 2-methyl-1 : 2 : 3 : 4-tetrahydroisoarsinoline (6·9 g.) and *o*-β-bromoethylbenzyl bromide (9·2 g., 1 mol.) when stirred readily formed a clear solution which within a few minutes became warm and then set to a viscous glass. The latter was then heated under reflux at 14 mm. pressure, the temperature being slowly increased to 200° and maintained there for 1 hour. The mixture effervesced just above 100° and began to darken, and a colourless liquid refluxed in the condenser. After 1 hour at 200°, crystallisation occurred, and heating for a further 1·5 hours at 200° made no perceptible change, although rapid refluxing of the volatile liquid continued. The latter was therefore distilled off (b. p. *ca.* 68°/17 mm.), and the residue extracted with boiling alcohol (25 c.c.) to which a few drops of aqueous hydrobromic acid had been added to give complete solution. The latter on cooling deposited the colourless crystalline *bromide* (VI), which was collected, washed with alcohol and ether, and dried (5 g., 38%); it was recrystallised from very dilute hydrobromic acid, or from alcohol, or from alcoholic ether; m. p. 288—290° (Found : C, 55·6; H, 5·3. $C_{18}H_{20}BrAs$ requires C, 55·25; H, 5·1%).

The above appear to be the optimum conditions for the preparation of the bromide : other experiments, in which the manner, time, and degree of heating were varied over wide limits, gave lower yields.

When a hot saturated alcoholic solution of the bromide was treated with a cold saturated alcoholic solution of sodium iodide, the dl-*arsinolinium iodide* separated on cooling as colourless crystals, which when recrystallised from alcohol had m. p. 231—233° with darkening from 225° (Found : C, 49·5; H, 4·8. $C_{18}H_{20}IAs$ requires C, 49·3; H, 4·6%).

Resolution of the Arsonium Ion.—Solutions of the bromide (VI) and of silver *d*-bromocamphorsulphonate (1 mol.), each in boiling 96% alcohol, were mixed, shaken to coagulate the silver bromide, filtered, and the solvent then removed under reduced pressure. The oily residue could not be obtained crystalline from any organic solvent; a solution in hot water (charcoal) on slow cooling, however, deposited the crystalline *d*-bromocamphorsulphonate, m. p. 70—74°; a 0·678% alcoholic solution had α + 0·88°, [*M*] + 202°. Successive recrystallisations from water gave the sulphonate at first as hydrated crystals which in a vacuum over sulphuric acid readily effloresced, affording the hygroscopic anhydrous salt, but after four recrystallisations as hydrated crystals which underwent similar dehydration but without apparent loss of their crystal form : the powdered anhydrous salt had necessarily to be weighed in a dry atmosphere. The data for the crops from the final crystallisations, after dehydration, were :

Total number of crystallisations.	M. p.	Concn. of alcoholic solution (g. solute/100 c.c. solution).	α.	[*M*].
4	185 —187°	0·824	+0·66°	+124°
5	184·5—186·5	1·005	+0·75	+116
6	186 —187	0·900	+0·69	+119

The optically pure l-*arsonium* d-*bromocamphorsulphonate* had therefore been isolated after 5 recrystallisations : the powdered dehydrated salt from the final recrystallisation on exposure to air formed a *monohydrate* (Found, for the anhydrous salt : C, 53·8; H, 5·5; Br, 13·2; increase in weight on exposure to air, 2·9. $C_{28}H_{34}O_4BrSAs$ requires C, 54·1; H, 5·5; Br, 12·9; increase in weight on monohydrate formation, 2·9%. Found, for the salt after exposure : C, 52·7; H, 6·1; Br, 13·5, 13·7. $C_{28}H_{34}O_4BrSAs,H_2O$ requires C, 52·6; H, 5·6; Br, 12·5%). A 0·928% alcoholic solution of the monohydrate had α + 0·69°, [*M*] + 119°.

1-As-spiro-*Bis*-1 : 2 : 3 : 4-*tetrahydroisoarsinolinium Iodide* (as VI).—When an ice-cold solution of the above sulphonate (0·7 g.) in alcohol (40 c.c.) was treated with an excess of a solution of sodium iodide in 95% alcohol, colourless needles of the l-*iodide* separated; these were collected, and washed with alcohol and ether; 0·42 g. A portion of this iodide, when dried in a vacuum, had m. p. 225—228°, and in 0·389% chloroform solution had α — 1·22°, [*M*] — 343°. The remainder, recrystallised from alcohol, separated as magnificent long needles, of unchanged m. p. (Found: C, 48·6; H, 4·4; I, 29·1. $C_{18}H_{20}IAs$ requires C, 49·3; H, 4·6; I, 29·0%); a 0·385% chloroform solution had α — 1·21°, [*M*] — 344°, these values remaining unchanged during one month at 18°. The full rotatory dispersion values are given on p. 46. It is clear from these results that the arsonium ion has a much greater rotation in chloroform than in alcoholic solution.

The d-*arsonium* l-*bromocamphorsulphonate*. The aqueous filtrates from the first three recrystallisations of the above *d*-bromocamphorsulphonate, when treated with aqueous potassium iodide, deposited the optically impure *d*-iodide. This was collected, dried, and, by treatment with silver *l*-bromocamphorsulphonate, converted into the arsonium *l*-bromocamphorsulphonate. Four recrystallisations from water afforded the optically pure d-*arsonium* l-*sulphonate*, m. p. 185—187° (Found for the dehydrated salt: C, 53·6; H, 6·11%); a 0·931% alcoholic solution had α — 0·73°, [*M*] — 123°. Further recrystallisation did not affect the rotation of this salt, which however always separated as a *hydrate* (Found: C, 52·05; H, 6·0; Br, 12·8%), which readily lost its water and crystalline form in a vacuum.

d-As-spiro-*Bis*-1 : 2 : 3 : 4-*tetrahydroisoarsinolinium Iodide* (as VI).—This *salt* was prepared from the *l*-sulphonate as previously described, and after recrystallisation from alcohol was obtained as long colourless needles, m. p. 226—228° (Found: C, 49·3; H, 4·4; I, 29·3. $C_{18}H_{20}IAs$ requires C, 49·3; H, 4·6; I, 29·0%); a 0·384% chloroform solution had α + 1·20°, [*M*] + 342°.

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15. *Reactions of Furan Compounds. Part II. Fission of the Tetrahydrofuran and the Tetrahydropyran Ring.*

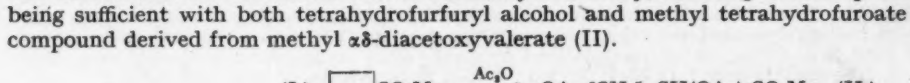
By CHRISTOPHER L. WILSON.

Various tetrahydrofuran compounds and tetrahydropyran with reagents such as acetic anhydride or hydrogen bromide give open-chain butane or pentane derivatives.

The fission reaction has been applied to tetrahydrofuran, tetrahydrofurfuryl alcohol, its acetate, chloride and bromide, methyl tetrahydrofuroate, acetotetrahydrofurfurylamide, and tetrahydropyran. Simple methods of preparation of the following compounds have been devised: 1 : 2 : 5-triacetoxy-, 1 : 2 : 5-trihydroxy-, 1 : 2 : 5-tribromo-, 1-*bromo*-5-*acetoxy*-, and 1 : 5-dibromo-*n*-pentane, 1 : 4-dibromobutane, 1-bromo-Δ^4-pentene, and 3-*bromopropylethylene oxide*.

PAUL (*Bull. Soc. chim.*, 1933, **53**, 417; 1941, **8**, 369; *Compt. rend.*, 1939, **208**, 587) appears to have carried out the first systematic experiments on the splitting of the ether linkages in the tetrahydro-furan and -pyran rings, and the present work is supplementary to his. The discussion is divided into sections according to the fission reagent.

Fission by Acetic Anhydride.—Paul (*loc. cit.*, 1933) investigated the reaction of tetrahydrofuran derivatives with acetic anhydride in the presence of zinc chloride as catalyst by heating the reactants in a sealed tube to 190—200°. He showed, *e.g.*, that tetrahydrofurfuryl alcohol is converted into 1 : 2 : 5-triacetoxypentane, but we find that use of a sealed tube is not always necessary, refluxing at atmospheric pressure for some time being sufficient with both tetrahydrofurfuryl alcohol and methyl tetrahydrofuroate (I). The latter gave a compound derived from methyl $\alpha\delta$-diacetoxyvalerate (II).



(I.) $\xrightarrow[ZnCl_2]{Ac_2O}$ $OAc\cdot[CH_2]_3\cdot CH(OAc)\cdot CO_2Me$ (II.)

Other compounds examined did not react well. Tetrahydrofurfuryl methyl ether gave methyl acetate and triacetoxypentane. Acetotetrahydrofurfurylamide was unaffected, but tetrahydrofuronitrile readily lost hydrogen cyanide and produced tarry material. Tetrahydrofurfuryl chloride and bromide gave complex mixtures containing mono-, di-, and tri-halides.

In these reactions it is likely that zinc chloride forms with acetic anhydride a complex which possesses a considerably enhanced tendency to lose a positively charged acetyl group. This group can then become attached to the ether oxygen atom and the oxonium compound produced, $\rangle\overset{+}{O}Ac\}\{ZnCl_2OAc\}^-$, undergoes degradation.

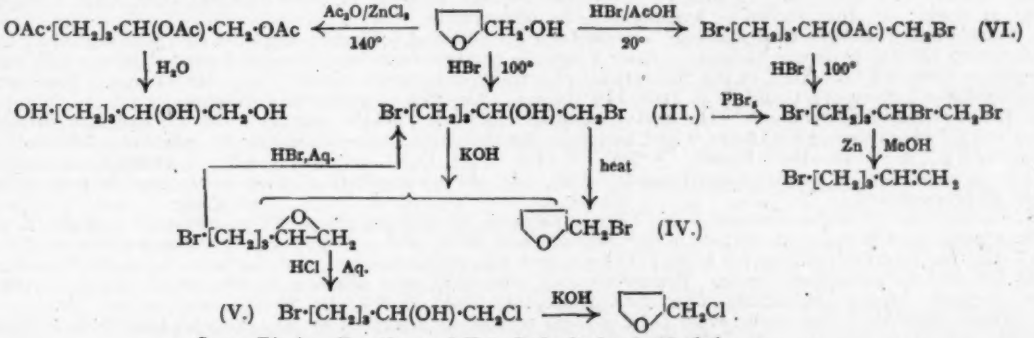
The intervention of an ionic complex is supported by the absence of reaction if the vapours of tetrahydrofurfuryl alcohol and acetic anhydride are passed at a high temperature over a catalyst containing zinc chloride. Under these conditions, in the absence of solvent, ionisation is undoubtedly suppressed and reaction cannot occur.

Fission by Hydrogen Halides.—Paul (*loc. cit.*, 1933) saturated tetrahydrofurfuryl alcohol with gaseous hydrogen bromide at 100° and obtained what he considered to be a mixture of isomeric dibromohydrins (III) and $OH\cdot[CH_2]_3\cdot CHBr\cdot CH_2Br$ (III*a*). We have further examined this reaction. Analysis of the crude product established the presence of two bromine atoms. It distilled in a vacuum with slight loss of hydrogen bromide, but when fractionation was attempted in the presence of stainless-steel Lessing rings, hydrogen bromide was rapidly evolved, and tetrahydrofurfuryl bromide (b. p. 56—58°/12 mm.) produced.

The crude dibromohydrin showed but little reaction with zinc, indicating the absence of the 4 : 5-dibromo-

compound (III*a*), and, in view of the easy cyclisation to tetrahydrofurfuryl bromide (above), the product must have consisted essentially of 1 : 5-dibromo-2-hydroxy-*n*-pentane (III). With phosphorus pentabromide, or under the prolonged action of hydrogen bromide, this produced 1 : 2 : 5-tribromopentane, which readily lost its two adjacent bromine atoms by reaction with zinc to give 1-bromo-Δ^4-pentene.

Paul (*Ann. Chim.*, 1932, **18**, 303) showed that 4 : 5-dibromo-*n*-amyl alcohol (III*a*) gave only tetrahydrofurfuryl bromide (IV) on reaction with potassium hydroxide, but we found that with this reagent the isomeric dibromo-compound (III) gave equal amounts of (IV) and an isomer, b. p. 74—76°/13·5 mm., which, unlike (IV), reacted with 15% hydrochloric or hydrobromic acid with heat evolution to give, respectively, a high-boiling chlorobromohydrin (V) or the dibromohydrin (III). It was concluded, therefore, that the isomer of (IV) was 3-*bromopropylethylene oxide*. The chlorobromohydrin (V) with potassium hydroxide produced mainly tetrahydrofurfuryl chloride, thus differing from the dibromohydrin (III), which gave about equal amounts of the ethylene oxide and tetrahydrofurfuryl bromide (IV).

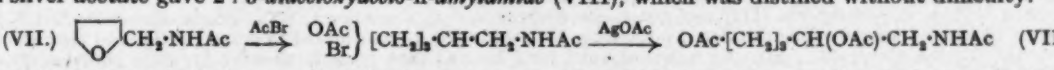


Some Fission Reactions of Tetrahydrofurfuryl Alcohol.

Tetrahydrofuran reacts readily with acetyl bromide at room temperature to give 4-bromobutyl acetate in 85% yield (Goldfarb *et al.*, *Chem. Abs.*, 1939, **33**, 4593; 1941, **35**, 4011; *A.*, 1941, ii, 74). Using, instead of acetyl bromide, a reagent prepared by saturating acetic anhydride with hydrogen bromide, we have now shown that tetrahydrofurfuryl acetate also suffers fission to give a mixture of mono- and di-bromo-compounds. With hydrogen bromide dissolved in acetic acid tetrahydrofurfuryl alcohol gave an excellent yield of a dibromoacetoxypentane, which, by its unreactivity towards zinc, was assumed to be 1 : 5-*dibromo*-2-*acetoxy*-n-*pentane* (VI). Paul has recently shown (*Chem. Abs.*, 1942, **36**, 751) that the same orientation in fission occurs when acetyl chloride is used.

We showed that methyl tetrahydrofuroate reacted readily at room temperature with acetic anhydride–hydrogen bromide. The product consisted of methyl acetate and bromide, a crystalline bromohydroxy-acid, m. p. 83—84°, assumed to be *δ-bromo-α-hydroxyvaleric acid* since it lost hydrogen bromide readily on heating to 140°, a bromoacetoxy-acid, and *methyl δ-bromo-α-acetoxyvalerate*, although this orientation is uncertain. It proved impossible to establish a relation between the acids and the ester, since hydrolysis of the latter always led to loss of bromine as well as acetoxyl group, but it is probable that all three compounds are related, the acids having resulted by partial hydrolysis of the ester under the conditions of reaction and isolation. The α-hydroxy-acid structure is confirmed by Paul (*Compt. rend.*, 1941, **212**, 398; *Chem. Abs.*, 1942, **36**, 6140), who has shown that fission of tetrahydrofuroic acid and its ethyl ester with acetyl chloride or hydrogen bromide in acetic acid proceeds exclusively in this direction.

Acetotetrahydrofurfurylamide (VII) in our experiments was readily attacked by acetyl bromide to give an open-chain bromoacetoxy-compound. This could not be distilled without decomposition, but reaction with silver acetate gave 2 : 5-*diacetoxyaceto*-n-*amylamide* (VIII), which was distilled without difficulty.



Fission of Tetrahydropyran.—Tetrahydropyran was about 100 times less reactive than tetrahydrofuran towards acetyl bromide. Nevertheless, it was possible to obtain a good yield of 5-bromo-*n*-amyl acetate by reaction at room temperature. At 100° in the presence of hydrogen bromide the acetoxyl group was slowly replaced by bromine to give pentamethylene dibromide. This compound was also produced by boiling tetrahydropyran with hydrobromic acid and sulphuric acid under reflux (cf. *Org. Synth.*, 1943, **23**, 67).

Experimental.

I. *Fission with Acetic Anhydride.* (a) *Tetrahydrofurfuryl alcohol.* Tetrahydrofurfuryl alcohol (306 g., 291 c.c., 3 g.-mols.) was added slowly to boiling acetic anhydride (1 kg.) containing anhydrous zinc chloride (5 g.) so as to keep the mixture refluxing. Boiling was continued for a further 24 hrs., and the product then distilled in a vacuum. 1 : 2 : 5-Triacetoxypentane (665 g., 90%) was obtained, b. p. 172—174°/17 mm. Low-boiling material contained tetrahydrofurfuryl acetate, b. p. 191—192°, which was separated by neutralising the acetic acid with sodium hydroxide. Attempts to carry out the fission as a vapour-phase reaction failed with either silica gel or zinc chloride deposited on pumice as catalyst.

1 : 2 : 5-*Trihydroxypentane.* 1 : 2 : 5-Triacetoxypentane (246 g., 1 g.-mol.) was refluxed with 0·1N-hydrochloric acid

(500 c.c.) for 3 hrs., and acetic acid then removed by steam-distillation. The residue was distilled in a vacuum, giving 1 : 2 : 5-trihydroxypentane as a viscous liquid, b. p. 180—182°/6 mm.; yield 60%. If steam-distillation was omitted, the product had b. p. 170—174°/10 mm. and saponification showed that it contained the equivalent of 70% of the mono-acetoxy-compound.

(b) *Methyl tetrahydrofuroate.* The ester (22·8 g.), acetic anhydride (65 g.), and zinc chloride (anhydrous, 0·5 g.) were refluxed for 15 hrs. The product was distilled in a vacuum, giving unchanged ester, b. p. 70°/13 mm. (7·5 c.c.), and a product, b. p. 115—160°/13 mm. (9·0 c.c.). The latter was shaken with aqueous sodium carbonate until neutral, and redistilled. Most of the distillate had b. p. 142—143°/14 mm.; it was saturated to bromine in aqueous acetic acid solution, and contained acetoxyl and carbomethoxyl groups. Carbon monoxide was evolved with warm concentrated sulphuric acid. Analysis (Found: C, 49·2; H, 6·9; Ac, 24·9; equiv., by saponification, 72. Calc. for $C_8H_{14}O_5$: C, 50·5; H, 7·4; Ac, 22·6%; equiv., 95) suggests the product was essentially a methyl hydroxyacetoxyvalerate. It is probable that the sodium carbonate treatment caused some hydrolysis of the diacetoxy-compound formed initially (Paul, *loc. cit.*, 1941).

(c) *Tetrahydrofuronitrile.* The nitrile (8·6 g.) was refluxed with acetic anhydride (15 g.) and zinc chloride (anhydrous, 0·2 g.). Hydrogen cyanide was rapidly evolved, and tarry material formed. Attempted distillation gave a small amount of a solid, b. p. 120—130°/12 mm., m. p. 74—76° [Found: C, 47·7; H, 7·1; *M* (Rast), 106. Calc. for $C_4H_7O_2N$: C, 47·5; H, 6·9%; *M*, 101], shown by hydrolysis to be diacetamide.

II. *Fission with Hydrogen Chloride.*—(a) *Tetrahydrofurfuryl alcohol.* The alcohol (48·5 c.c.) was heated to 150° and saturated with gaseous hydrogen chloride. After 9 hrs. the product contained unreacted alcohol (about 25%) together with variable amounts (12—25% of the theoretical) of tetrahydrofurfuryl chloride, b. p. 40°/14 mm. The rest of the product consisted largely of a liquid, b. p. 110—140°/10 mm. (20—25% of product by weight).

(b) *Acetotetrahydrofurfurylamide.* The acetyl compound (28·6 g.), acetic anhydride (35 g.), and zinc chloride (anhydrous, 0·5 g.) were refluxed for 15 hrs. whilst hydrogen chloride (10 g.) was passed into the mixture. Distillation gave a product (6·8 g.), b. p. 160—190° (Found: N, 7·6; Cl, 14·5. $C_9H_{16}O_3NCl$ requires N, 6·3; Cl, 16·0%), probably mainly *aceto*-[2(or 5)-*chloro*-5(or 2)-*acetoxy*-n-*amyl*]*amide*. This, like the corresponding bromo-compound, was miscible with water in all proportions.

III. *Fission with Hydrogen Bromide.*—(a) *Tetrahydrofuran.* Tetrahydrofuran (72 g., 80 c.c., 1 g.-mol.), b. p. 64—66·5°, was added slowly to a cold mixture of hydrobromic acid (50%, 972 g., 6 g.-mols.) and concentrated sulphuric acid (50 c.c.), and the mixture refluxed for 3 hrs. The product was steam-distilled, and the lower layer dried over calcium chloride followed by phosphoric oxide. Tetramethylene dibromide, thus obtained in 82% yield, had b. p. 198—201° (Found: C, 22·8; H, 3·8; Br, 72·35. Calc. for $C_4H_8Br_2$: C, 22·2; H, 3·7; Br, 74·0%).

(b) *Tetrahydropyran.* The cyclic ether (17·2 g.) was treated as described in (a). The pentamethylene dibromide, obtained in 78% yield, had b. p. 106—108°/19 mm.

Tetrahydrofurfuryl alcohol and methyl tetrahydrofuroate did not undergo fission under similar conditions.

(c) *Tetrahydrofurfuryl alcohol and gaseous hydrogen bromide.* The alcohol (48·5 c.c.) was heated to 100°, and hydrogen bromide passed in until the increase in weight was 80—85 g. (6 hrs.). The product was poured into water, and the lower layer (100—115 g.) separated (Found: Br, 56·6%). About 90 g. of this distilled with slight decomposition at 120—140°/12 mm. A dibromohydroxypentane would require Br, 65%, and a bromodihydroxypentane Br, 43·7%.

The crude dibromohydrin was mixed with zinc in the presence of methyl alcohol. Very little reaction occurred in the cold, and heating under reflux produced only a slow evolution of hydrogen, indicating the absence of appreciable amounts of the 1 : 2-dibromo-compound.

Conversion of the dibromohydrin (III) *into tetrahydrofurfuryl bromide* (IV). The crude dibromohydrin was heated in a vacuum in a Claisen flask having a 4″ fractionating column packed with stainless-steel rings. The distillate was redistilled, giving tetrahydrofurfuryl bromide (34 g.), b. p. 57—64°/12 mm. The yield calculated on the alcohol used (51 g.) was 41%. In another experiment the fractionating column was omitted but a few of the metal rings were added to the crude dibromohydrin (37 g.). The product consisted of tetrahydrofurfuryl bromide, b. p. 56—58°/12 mm., 16 g., 64% (Found: C, 36·8; H, 5·6; Br, 47·7. Calc. for C_5H_9OBr: C, 36·4; H, 5·5; Br, 48·5%), and a liquid, b. p. 130—140°/12 mm., which, from its vigorous reaction with zinc and its bromine content (75·0%), was mainly 1 : 2 : 5-tribromopentane (Br, 77·7%).

Conversion of dibromohydrin (III) *into* 1 : 2 : 5-*tribromopentane.* The crude dibromohydrin was treated with phosphorus pentabromide suspended in carbon tetrachloride (cf. *Org. Synth.*, 1933, **13**, 21). When hydrogen bromide ceased to be evolved the product was decomposed carefully with water and distilled. 1 : 2 : 5-Tribromopentane, b. p. 130—132°/16 mm., was obtained in 46·2% yield calculated on the alcohol taken. Von Braun and Köhler (*Ber.*, 1918, **51**, 93) give b. p. 128—132°/11 mm.

1-*Bromo*-Δ^4-*pentene from tribromopentane.* The tribromo-compound (126 g.) was added slowly to zinc (needles, 34·1 g.) covered with methyl alcohol (50 c.c.). The very vigorous reaction was completed by refluxing with external heating for 0·5 hr. Water was added, and the lower layer distilled after drying over calcium chloride; b. p. 127—129°/770 mm. (41·4 g., 71·2%). The zinc consumed (24·8 g.) corresponded with a 72% yield of 1-bromo-Δ^4-pentene (Found: Br, 53·0. Calc. for C_5H_9Br: Br, 53·6%). Von Braun and Köhler (*loc. cit.*) give b. p. 110°, obviously in error, since 127—129° agrees with Gaubert, Linstead, and Rydon's b. p. (J., 1937, 1972).

Reaction between dibromohydrin (III) *and potassium hydroxide.* (i) No solvent. The crude dibromohydrin (89 g.) was cooled in ice and stirred while powdered potassium hydroxide (30 g.) was added in small portions so that the temperature did not rise above 30°. Stirring was continued for 1 hr. and then for a further 0·5 hr. after addition of water (30 c.c.). More water was added, and the organic layer separated and distilled. Two fractions were obtained: (1) b. p. 78—82°/17 mm. (47 g.); (2) b. p. 110—140°/18 mm. (2·5 g.). The latter reacted violently with zinc and was probably mainly 1 : 2 : 5-tribromopentane. A portion (36 g.) of fraction (1) was shaken with hydrochloric acid (15%); much heat was evolved, and the product was washed with water and distilled, giving: (*a*) b. p. 65—67°/18 mm. (13·6 g.; tetrahydrofurfuryl bromide); (*b*) b. p. 113—120°/18 mm. (slight decomp.; 7·6 g.); (*c*) b. p. 126—135°/17 mm. (7·7 g.). Fractions (*b*) and (*c*) were treated with powdered potassium hydroxide, and the product washed with water and distilled. It gave tetrahydrofurfuryl chloride, b. p. 51—56°/17 mm. (5·5 g.), and a compound, b. p. 75—80°/17 mm. (2·7 g.), which again became hot on treatment with hydrochloric acid.

(ii) In dioxan. The above reaction of the crude dibromohydrin (90 g.) with potassium hydroxide was repeated in the presence of dry dioxan (100 c.c.). The product, b. p. 75—82°/17 mm. (50 g.), was treated with cold hydrobromic acid (50%), and distillation afforded 3·0 g., b. p. 61—64°/17 mm. (tetrahydrofurfuryl bromide), and 16·5 g., b. p. 120—140°/12 mm. (slight decomp.).

A large amount of the product obtained by reaction of the crude dibromohydrin with potassium hydroxide was fractionated through a 10″ column packed with stainless-steel rings, giving (*a*) b. p. 56—58°/12 mm., tetrahydrofurfuryl bromide, and (*b*) b. p. 74—76°/13·5 mm., which by its analysis (Found: C, 36·2; H, 5·35; Br, 48·4. C_5H_9OBr requires C, 36·4; H, 5·5; Br, 48·5%) and reactions with aqueous acids is considered to be 3-*bromopropylethylene oxide*.

The reactions described under (*a*) and (*b*) above suggest that in the absence of solvent the crude dibromohydrin gives

approximately equal amounts of the furan and the ethylene oxide derivative, whereas in the presence of dioxan the latter preponderates (7·4 : 2). In contrast to the dibromohydrin, the chlorobromohydrin (from the ethylene oxide and hydrochloric acid) on cyclisation with potassium hydroxide gives mainly tetrahydrofurfuryl chloride.

IV. *Fission with Hydrogen Bromide in Acetic Acid.*—The reagent was prepared by saturation of acetic acid at 20° with hydrogen bromide, generated by reaction of bromine with boiling tetralin. It contained 35·9% of hydrogen bromide and had *d* 1·34.

(a) *Tetrahydrofurfuryl alcohol.* The hydrogen bromide solution (175 c.c.) and the alcohol (48·5 c.c.) were mixed with cooling and left for 14 hrs. at room temperature. The product (116 g., 81%), isolated by pouring into water and washing with aqueous alkali, had b. p. 139—144°/11 mm. (Found : C, 29·55; H, 4·4; Br, 54·3, 54·6. $C_7H_{13}O_2Br_3$ requires C, 29·2; H, 4·2; Br, 55·6%), and its analysis, reaction with zinc (below), and method of formation indicate it to be 2 : 5-*dibromo*-n-*amyl*·*acetate*.

Reaction with zinc. This compound (39 g.) was added to zinc (10 g.) in methyl alcohol (30 c.c.). There was no perceptible reaction in the cold. On boiling, a very slow evolution of hydrogen ensued, but after 2 hrs. only 1·5 g. of the zinc had been consumed. The product gave on distillation (i) b. p. 170—174°/775 mm., 65—68°/12 mm., 10 g. (Found : Br, 46·7. Calc. for C_5H_9OBr : Br, 48·5%), probably tetrahydrofurfuryl bromide, and (ii) b. p. 143—144°/11 mm., 12·5 g. (Found : C, 29·5; H, 4·3; Br, 54·5%), unchanged dibromoamyl acetate.

(b) *Tetrahydrofurfuryl alcohol at* 100°. The product from the alcohol (48·5 c.c.) and hydrogen bromide in acetic acid was heated to 100°, and a slow stream of hydrogen bromide introduced. After 8 hrs. the product, worked up as above, gave 90 g., b. p. 125—135°/8 mm., which, from its reaction with zinc, contained much tribromopentane. 89 G. of the product were treated with zinc, of which 12 g. reacted in 20 minutes, corresponding with 57 g. of tribromopentane. The product on distillation gave (i) b. p. 128—130°, 25 g. (Found : Br, 50·65. Calc. for C_5H_9Br : Br, 53·7%), essentially 1-bromo-Δ^4-pentene, and (ii) b. p. 149—153°/17 mm., 11·5 g. (Found : Br, 54·6. Calc. for $C_5H_9OBr_2Ac$: Br, 55·6%), mainly unchanged dibromoamyl acetate. A small intermediate fraction (3·5 g.), b. p. 60—77°/18 mm., may have been tetrahydrofurfuryl bromide.

V. *Fission with Hydrogen Bromide in Acetic Anhydride* (*Acetyl Bromide*).—The reagent, prepared by saturation of acetic anhydride at 20°, contained 50·9% of hydrogen bromide and had *d* 1·54. It may be considered to be a mixture of acetic anhydride, acetyl bromide, acetic acid, and hydrogen bromide.

(a) *Tetrahydrofurfuryl acetate.* The ester (53 g.) was mixed with the hydrogen bromide solution and kept at room temperature for 18 hrs. Isolated in the usual way, the product (55 g.) had b. p. 140—144°/8 mm. and was a mixture (Found : Br, 45·7. Calc. for $C_5H_9OBrAc_2$: Br, 30·0%. Calc. for $C_5H_9OBr_2Ac$: Br, 55·6%).

(b) *Methyl tetrahydrofuroate.* The ester (31 g.) was mixed under cooling with the acetic anhydride reagent (55 c.c.) and kept at room temperature for 48 hrs. The solution was poured into water, and the lower layer shaken with sodium hydroxide solution (5%) until free from acid. Distillation gave 45 g., b. p. 140—143°/10 mm. (Found : Br, 29·3; Ac, 18·0. $C_9H_{13}O_4Br$ requires Br, 31·6; Ac, 17·0%). In the early stages of the distillation low-boiling material was caught in a Drikold–acetone trap. It contained an acetoxyl group and formed a quaternary bromide with pyridine and was, therefore, evidently a mixture of methyl acetate and bromide.

The alkali wash obtained above was acidified, giving an oil (8 g.) which partly solidified on standing. The liquid portion contained an acetoxyl residue but the solid, which crystallised from benzene in colourless plates, m. p. 83—84°, and decomposed at 140° evolving hydrogen bromide, contained bromine but not acetoxyl (Found : C, 30·65; H, 4·45; Br, 39·55. $C_5H_9O_3Br$ requires C, 30·5; H, 4·6; Br, 40·6%). In view of the reactions and the evidence quoted earlier in discussion, it is highly probable that the ester, acetoxy-acid, and acetoxyl-free acid represent successive stages of hydrolysis and are respectively *methyl δ-bromo-α-acetoxyvalerate*, δ-bromo-α-acetoxyvaleric acid, and *δ-bromo-α-hydroxyvaleric acid*.

(c) *Acetotetrahydrofurfurylamide.* The acetyl derivative (13·4 c.c., 14·3 g., 0·1 g.-mol.) and hydrogen bromide in acetic anhydride (30 c.c.) were mixed and kept for 2 hrs. The solid product was treated with aqueous sodium hydroxide (30%) with cooling until neutral. The organic layer was separated by ether extraction. Extensive decomposition occurred on attempted distillation, with loss of hydrogen bromide and acetic acid. Analysis of the crude material, however, indicated that the expected fission product, *bromoacetoxyacetopentylamide*, had been obtained (Found : N, 5·55; Br, 27·05; Ac, 29·6. $C_9H_{16}O_3NBr$ requires N, 5·3; Br, 30·1; 2Ac, 32·3%).

The crude fission product was heated to 100° with excess of silver acetate in glacial acetic acid for 2 hrs. The weight of silver bromide produced indicated that 70% of the bromine had been replaced. The product, distilled with a little decomposition, b. p. 170—193°/3 mm., still contained bromine (Found : Br, 10·8%). Another sample of the crude fission product was heated with silver acetate with stirring for 24 hrs. The product, b. p. 175—185°/3 mm., contained very little bromine (Found : Br, 0·7%) and was mainly 2 : 5-*diacetoxyaceto*-n-*amylamide* (Found : Ac, 52·0. $C_{11}H_{19}O_5N$ requires 3Ac, 52·6%). This compound, like the crude bromo-diacetyl derivative, was completely miscible with water although it was readily salted out.

(d) *Tetrahydropyran.* After 5 days at room temperature tetrahydropyran with hydrogen bromide in acetic acid gave a product, b. p. 97—102°/9 mm. (Found : C, 35·2; H, 5·75; Br, 47·95; Ac, 12·9%). The substance being assumed to be a mixture of bromoacetoxy- and dibromo-pentane, the analysis indicates that 29 mols. % of the latter were present.

After 8 days with hydrogen bromide in acetic anhydride, the product contained 13 mols. % of the dibromide (Found : Br, 42·75%). From 48 g. of tetrahydropyran and 60 c.c. of acetic anhydride solution after 6 days the product consisted of unchanged pyran (15 g.), and 5-*bromo*-n-*amyl acetate* (1-*bromo*-5-*acetoxy*-n-*pentane*), b. p. 109—110°/15 mm. (Found : Br, 39·1. $C_7H_{13}O_2Br$ requires Br, 38·2%), containing only 2·5 mols. % of dibromide. These are considered to be the best conditions for preparing this acetate.

On heating the pyran in acetic acid under reflux for 6 hrs. whilst hydrogen bromide was passed in, a product was obtained, b. p. 98—99°/10 mm., 61 g. (Found : Br, 67·75%), containing only 6 mols. % of bromoamyl acetate.

Preparation of Tetrahydrofurfuryl Chloride.—Tetrahydrofurfuryl alcohol and phosphorus trichloride either alone or in pyridine failed to afford the chloride. Kirner (*J. Amer. Chem. Soc.*, 1930, **52**, 3251), using thionyl chloride in pyridine, obtained a 75% yield after considerable trouble. Omitting pyridine, we have found that thionyl chloride alone gives a 46% yield. The alcohol (10·2 g., 0·1 g.-mol.) was heated to 100°, and thionyl chloride (80 c.c.) added slowly. The mixture was then distilled in a vacuum, and the product, b. p. <100°, washed with sodium hydroxide solution (15%). Tetrahydrofurfuryl chloride, b. p. 152—154°, was insoluble and could be dried over anhydrous potassium carbonate. The low yield appears to be due to the formation of a chlorosulphite.

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16. *Reactions of Furan Compounds. Part III. Formation of Tetrahydrofuran, 2 : 3-Dihydrofuran, and Other Substances by Passage of Tetrahydrofurfuryl Alcohol Vapour over a Nickel Catalyst.*

By Christopher L. Wilson.

The side chain of tetrahydrofurfuryl alcohol is eliminated as carbon monoxide and hydrogen to give tetrahydrofuran and 2 : 3-*dihydrofuran* when the vapour is passed over a nickel or nickel-containing catalyst above 200°.

By-products include propylene, furan, butyl alcohol, methyl *n*-propyl ketone, and *tetrahydrofuryl tetrahydrofurfuryl ether*. Their formation is discussed.

The new reaction now described was the outcome of attempts to open the tetrahydrofuran ring by catalytic reduction. In the belief that the most drastic conditions which could be applied were those of Sabatier and Senderens's method, the vapour of tetrahydrofurfuryl alcohol, together with hydrogen, was passed over reduced nickel. This alcohol was chosen as the most readily available tetrahydrofuran compound. There was no reaction at 200°, but at 265° a vigorous decomposition ensued, marked by the evolution of gases not condensed at − 78°. The liquid product was shown to consist mainly of tetrahydrofuran. Omission of the added hydrogen did not inhibit the reaction, and in this case the gaseous products consisted of carbon monoxide and hydrogen in approximately equimolecular proportion. The reaction is represented by the equation $C_4H_7O{\cdot}CH_2{\cdot}OH \longrightarrow C_4H_8O + CO + H_2$.

The rest of this paper is concerned with some of the more important features of the reaction, such as the nature of the catalyst and the products.

Activity of Different Materials as Catalysts.—It was soon evident that only catalysts containing nickel were effective. Finely divided iron, cobalt, and copper were useless. Chromium oxide deposited on activated alumina, a catalyst usually associated with dehydrogenation processes, also failed to give any tetrahydrofuran.

Many different types of catalyst containing nickel were made. The most effective was prepared by packing the catalyst tube with rolls of nickel gauze which was active after the surface had been converted into finely divided metal. Since nickel is not readily oxidised even at a red heat, the gauze was treated with chlorine at 500°, and the surface layer of chlorides reduced with hydrogen. Another satisfactory catalyst was prepared by reducing nickel oxide deposited on granulated pumice: the substitution of silica gel for pumice gave an inferior catalyst. Nickel chromite was rather poor.

Catalysts containing other metals in addition to nickel were also investigated. One of these, prepared by reducing a mixture of nickel, copper, and manganese oxides on pumice, behaved like pure nickel except that its activity decreased rather more rapidly in use.

The most useful catalytic materials were prepared from nickel alloys. Those investigated had the following compositions: Monel metal (Ni, 66·5; Cu, 30·0%), "Ferry" alloy (Ni, 43·9; Cu, 54·3%), cupronickel (Ni, 19·7; Cu, 80·3%), Raney alloy (Ni : Al about 50 : 50), "Permalloy" (Ni, 78·3; Fe, 21·4%), "Brightray" (Ni, 78·0; Cr, 20·0%). Like pure nickel gauze, each alloy had to be activated before it showed any catalytic effect. Raney alloy and Brightray were resistant to high-temperature oxidation, but the former was converted into an extremely active nickel by treatment with hydrogen chloride at 450°, which removed aluminium without, apparently, disrupting the granular form of the alloy. Attempts to activate Brightray wire by chlorination failed; a vigorous reaction ensued to give a mixture of powdered metal chlorides with complete disintegration of the structure. The alloys containing iron and copper were all readily activated by oxidation at 550°, followed by reduction at a lower temperature.

Deterioration and Reactivation of Catalysts.—During the passage of tetrahydrofurfuryl alcohol over each catalyst, activity as measured by consumption * of alcohol slowly fell off. It was simple, however, to reactivate a deteriorated catalyst by oxidation at 550°, followed by reduction at 330°. With some of the alloy catalysts successive reactivations gave not only gradually increasing amounts of water at the reduction stage, but also gradually increasing consumptions of alcohol. A deteriorated catalyst could also be reactivated by a stream of hydrogen at a high temperature, but the catalyst so produced did not have as long an active life as one regenerated by oxidation and reduction.

Products of the Reaction.—In addition to carbon monoxide and hydrogen, the exit gases from the catalyst tube contained some propylene and a little propane. There were no indications, however, of the formation of C_4 hydrocarbons. The liquid product was distilled, and many of its constituents identified and estimated by methods described in the experimental section. Tetrahydrofuran was the major constituent of the fraction of b. p. < 160°. A cut was made at this temperature because it divided material containing all the tetrahydrofuran from a residue consisting mainly of unchanged alcohol. Some of the constituents of the low-boiling fraction from a nickel-on-pumice catalyst are indicated in Table I. In Table II a comparison of different catalysts is made.

The origin of some of the more interesting by-products is discussed below.

2 : 3-*Dihydrofuran.*—This compound is new. It was detected in the tetrahydrofuran by formation of

* In this paper "consumption" refers to the proportion of alcohol used up in a single passage over the catalyst. In the tables it is given as a percentage. "Yield" is estimated as a percentage of the theoretical yield based on consumption and not on input.

TABLE I.

Composition of crude tetrahydrofuran (b. p. <160°) from a nickel-on-pumice catalyst.

Substance.	% by wt.	Substance.	% by wt.
Furan	3·4	*n*-Butyl alcohol	1·5
Tetrahydrofuran	61·8	Crotyl (?) alcohol	0·5
2 : 3-Dihydrofuran	5·0	*cyclo*Pentanone	0·4
n-Butaldehyde	9·9	Water	6·3
Methyl *n*-propyl ketone	0·6	Tetrahydrofurfuryl alcohol	2·8

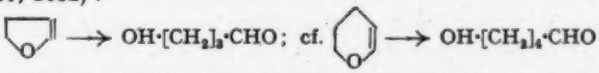
TABLE II.

Chief constituents (wt.-%) of crude tetahydrofuran (b. p. <160°) from a nickel gauze and various alloy catalysts.

Substance.	Ni gauze.	Monel metal.	" Ferry " alloy.	Raney alloy.	" Perm-alloy." *
Furan	3·0	—	3·0	3·5	—
Tetrahydrofuran	63·0	52	47	58·5	41
2 : 3-Dihydrofuran	3·5	12	20	6·5	12
n-Butaldehyde	9	3	5	5	4
Water	6	5	6	6	4

* This catalyst consisted of nickel and iron oxide.

γ-hydroxybutaldehyde-2 : 4-dinitrophenylhydrazone. The hydrolysis of 2 : 3-dihydrofuran to γ-hydroxybutaldehyde under the conditions employed is analogous to that of dihydropyran to δ-hydroxyvaleraldehyde (Paul, *Compt. rend.*, 1933, **197**, 1652) :



Absence of *s*-dihydrofuran was indicated by the equivalence of catalytic hydrogen absorption with the amount of precipitate given by Brady's reagent.

Reference to Table II indicates that, although the amount of dihydrofuran varies widely with different catalysts operating under optimum conditions, the yield of hydrogenated furans, *i.e.*, a mixture of only di- and tetra-hydrofuran, remains fairly constant (43±4%). This could mean that dihydrofuran is formed largely at the expense of tetrahydrofuran. Subsidiary experiments, however, showed that tetrahydrofuran is not dehydrogenated to dihydrofuran by passage over active nickel or " Ferry " alloy, and the dihydrofuran must, therefore, arise in some other way. The situation regarding the dehydrogenation-decarbonylation of simple aliphatic alcohols to hydrocarbons is somewhat similar. Experiment here, too, has shown that the olefin which is frequently observed is not produced by dehydrogenation of the saturated hydrocarbon (Badin, *J. Amer. Chem. Soc.*, 1943, **65**, 1809; Suen and Fan, *ibid.*, p. 1243). Böeseken and van Senden (*Rec. Trav. chim.*, 1913, **32**, 23) suggested that olefin arose by elimination of formaldehyde from the alcohol, but in our experiments there is certainly no support for this hypothesis.

Some interesting variations in the amount of dihydrofuran, C_4H_6O, formed by different catalysts are indicated in Tables II and III, the latter relating to the composition of the hydrogenated furan mixture containing only 2 : 3-di- and tetra-hydrofuran.

TABLE III.

Dihydrofuran content of hydrogenated furan mixture from various catalysts.

Catalyst.	C_4H_6O, %.	Catalyst.	C_4H_6O, %.
Raney nickel	1·0	" Permalloy " (Ni, Fe oxide)	23·1
Ni gauze (atm. press.)	4·0	,, (Ni, Fe)	28·6
Ni on pumice	4·1	" Ferry " alloy	30·4
Ni on silica gel	11·2	Cupronickel	37·7
Monel metal	18·3		

Too much attention should not be paid to the absolute value of the dihydrofuran data, since with any one catalyst its formation varied with activity. Progressive fall in activity, as measured by consumption of alcohol, was accompanied by a steady rise in dihydrofuran content of the hydrogenated furan mixtures; *e.g.*, when the activity of nickel had fallen to half its initially high value the dihydrofuran yield was about doubled. The data in Table III refer to freshly reactivated catalysts before deterioration became appreciable. Similar effects were noticeable amongst the nickel–copper alloys : as the copper content increased, the active life decreased and, as Table III shows, the dihydrofuran yield also increased. The effect of pressure on dihydrofuran formation with nickel is referred to later.

The variations in the amount of dihydrofuran formed under different conditions could, perhaps, be explained by assuming that this substance was intermediate in the formation of tetrahydrofuran, the catalyst having to fulfil the rôle of facilitating both the formation and the reduction of dihydrofuran. This leaves unexplained why dihydrofuran should be the primary product of side-chain elimination.

Tetrahydrofuryl Tetrahydrofurfuryl Ether.—The formation of this *compound* might be connected with that of dihydrofuran. It was isolated as a liquid, b. p. 101—102°/11 mm., from the high-boiling fractions of the

reaction product, and the important clue to its structure was the identification of its hydrolysis products with dilute acid as γ-hydroxybutaldehyde (dinitrophenylhydrazone identical with that from dihydrofuran) and tetrahydrofurfuryl alcohol: $C_4H_7O\cdot CH_2\cdot O\cdot C_4H_7O \longrightarrow C_4H_7O\cdot CH_2\cdot OH + OH\cdot[CH_2]_3\cdot CHO$.

Furan and Methyl n-*Propyl Ketone*.—Experiment showed that tetrahydrofuran was not dehydrogenated by a nickel catalyst to furan. The most plausible explanation for the presence of a small amount of furan in the reaction product is that it was formed from a trace of furfuryl alcohol present as impurity in the tetrahydrofurfuryl alcohol used. The presence of such an impurity has not been definitely proved by isolation, but it would explain this and three other observations: (i) the darkening of the alcohol by addition of a little concentrated hydrochloric acid, a reaction indicative of a furan compound (furfuraldehyde was shown to be absent); (ii) the presence of a small amount of furfuraldehyde, which might arise by dehydrogenation of furfuryl alcohol, in the reaction product from the nickel–copper alloys; (iii) the formation of a little methyl *n*-propyl ketone, the presence of which would be hard to explain if it were not for Padoa and Ponti's demonstration (*Gazzetta*, 1907, **37**, 105) that it is formed by Sabatier–Senderens reduction of furfuryl alcohol.

Both furan and methyl *n*-propyl ketone are assumed, therefore, to have arisen from furfuryl alcohol, which is a likely impurity, since tetrahydrofurfuryl alcohol is manufactured by catalytic reduction of furfuraldehyde.

Butyl Alcohol and n-*Butaldehyde*.—The original tetrahydrofurfuryl alcohol was shown to contain up to 1% of butyl alcohol (see p. 57), which is scarcely sufficient to account for that present in the reaction product, and still less for the butaldehyde. This conclusion was confirmed by the demonstration that butyl alcohol was readily decomposed to gaseous products (propane, propylene) by an active nickel catalyst and would not, therefore, withstand passage over the nickel without considerable loss.

The butyl alcohol fraction of the reaction product also contained an unsaturated alcohol. Its structure is uncertain but it is provisionally assumed to be crotyl alcohol (b. p. 117—120°) from the distillation range, 115—120°, of the fraction containing butyl alcohol. The presence of allylcarbinol is not excluded.

These alcohols probably arise by reductive fission of the hydrogenated furans, but confirmation is lacking.

cyclo*Pentanone and Tetrahydrofurfuraldehyde*.—Since the loss of the side chain of tetrahydrofurfuryl alcohol probably proceeds *via* the aldehyde (cf. Wojcik and Adkins, *J. Amer. Chem. Soc.*, 1933, **55**, 1293), it was remarkable that no trace of tetrahydrofurfuraldehyde could be found in the product from a nickel catalyst, although a special search was made for it. Later, however, it was shown, by formation of the dinitrophenylhydrazone, to be present to a very small extent in the product from a nickel catalyst operating under reduced pressure or from the alloys " Ferry ", cupronickel and " Permalloy " employed at ordinary pressure. Surprisingly enough, with Monel metal, as with nickel at ordinary pressure, the fractions which might have contained the aldehyde gave instead only the dinitrophenylhydrazone of *cyclo*pentanone. No adequate explanation for the presence of *cyclo*pentanone can be given. A careful search was made for *cyclo*pentanol, a possible precursor of the ketone, in the original alcohol, but without success. The only hydroxy-compound which was isolated boiling between 100° and 150° was butyl alcohol.

Effect of Temperature.—With each of the catalysts studied, increase of temperature caused a rise in consumption of alcohol. Between 200° and 300° this usually rose from a very low figure to 100%. On the other hand, the yield of hydrogenated furans, calculated after allowance for recovered alcohol, was at a maximum between 245° and 280°.

Data for a nickel gauze catalyst are in Table IV. This catalyst was, perhaps, the most satisfactory for semi-quantitative studies, since its hold-up was very small and its deterioration in use not too rapid. The whole series of experiments, each of which corresponds with an input of 0·25 g.-mol. of alcohol, was carried out without reactivation. " Consumption " and " yield " have the significance given to them on p. 52 (footnote).

TABLE IV.

Effect of temperature on the formation of hydrogenated furans from tetrahydrofurfuryl alcohol: nickel gauze catalyst.

(Input: 0·5 g.-mol./hr. Each expt. used 0·25 g.-mol. Activation of catalyst before the series by oxidation and reduction gave 8·5 c.c. of water.)

Expt.	1	2	3	4	5	6
Temp. (± 5°)	300°	300°	260°	280°	240°	300°
Alcohol consumed (%)	99	98	73	93	33	97
Hydrogenated furans,* yield (%)	17	20	45	39	43	28

* About 96% tetrahydrofuran.

It is noticeable that, whereas consumption rose progressively with temperature, yield attained a maximum at about 260°. Deterioration of the catalyst is just perceptible from a comparison of expts. nos. 1, 2 and 6; the gradual fall in activity is not sufficient, however, to obscure the effect of temperature.

Reactivation of the nickel gauze catalyst by hydrogen has already been mentioned. The effect of varying temperature with this catalyst was to produce a maximum yield of 50% at 280°.

The other catalysts all deteriorated more rapidly than nickel gauze, and the effect of temperature with each was not followed in detail. However, with activated Raney alloy the maximum yield (39%) was obtained at 245° with a consumption of 52%, and with the nickel–copper alloys, Monel and Ferry, the highest yield (45%) was obtained at about 290°.

Consumption and active life with cupronickel and Permalloy were too small to permit temperature variation to be followed.

Effect of Rate of Alcohol Input.—The nickel gauze catalyst being used, it was shown that increase in rate of alcohol input reduced consumption, and to a lesser extent, yield (see Table V).

TABLE V.

Effect of input on formation of hydrogenated furans from tetrahydrofurfuryl alcohol : nickel gauze catalyst.

(Temperature, 260° ± 5°. Each expt., 0·25 g.-mol. Catalyst gave 8·5 c.c. of water by oxidation and reduction.)

Input (g.-mol./hr.)	0·25	0·35	1·1	2·5
Alcohol consumed (%)	84	65	49	38
Hydrogenated furans,* yield (%)	43	45	43	35

* About 96% tetrahydrofuran.

Influence of Carrier Gases.—Large volumes of carbon monoxide and hydrogen are produced during the reaction; it is not surprising, therefore, that with nickel gauze the addition of further hydrogen only had the effect of lowering consumption, due, presumably to reduced time of contact between alcohol and catalyst. Carbon dioxide behaved similarly. In the present work carrier gas was not usually introduced during the reaction but only to sweep out the catalyst chamber after an experiment.

Effect of Pressure.—A few experiments were carried out under reduced pressure. The apparatus used did not permit a detailed study of the effect of pressure on the reaction but the results obtained (Table VI) showed that the optimum working temperature, about 225°, was somewhat lower than that, about 260°, obtaining at atmospheric pressure. The catalyst deteriorated more rapidly, however.

TABLE VI.

Effect of pressure on formation of hydrogenated furans : nickel catalyst.

(Input 0·5 g.-mol./hr. Each expt., 0·5 g.-mol. Water from activation, 8·6 c.c.)

Temp. (± 5°)	250°	270°	225°
Pressure (mm. Hg)	250 ± 100	300 ± 30	120 ± 40
Alcohol consumed (%)	63	94	52
Hydrogenated furans, yield (%)	38	26	43

Perhaps the most interesting feature of these experiments was the large amount—in the experiment at 225° it was 25·5%—of 2 : 3-dihydrofuran present in the hydrogenated furan mixture produced. There was also evidence that the amount of butaldehyde produced was lower than in the experiments at ordinary pressure. This suggests that some at any rate of the aldehyde probably arises by reductive fission of dihydrofuran.

EXPERIMENTAL

I. *Preparation of Catalysts.*—(a) *Nickel on silica gel.* Silica gel (150 g.), freed from sulphur compounds by boiling with concentrated nitric acid, followed by thorough washing with water, was stirred into a hot mixture of nickel nitrate (hexahydrate, 100 g.), nickel carbonate (50 g.), and water (50 c.c.). The mass was kept hot on a steam-bath and frequently stirred until it became crumbly. It was then packed into the catalyst tube, heated slowly to 400°, and when water and nitrogen oxides ceased to be evolved, reduced with hydrogen.

(b) *Nickel–copper–manganese oxides on pumice.* Copper nitrate (22 g.), manganese nitrate (142 g.), and nickel nitrate (126 g.), all as hexahydrates, were dissolved in hot water (100 c.c.), and pumice (8—16 mesh, 100 g.) added. The mixture was stirred at 100° until it was sufficiently dry to be packed into the catalyst tube, and then reduced at 400°.

(c) *Nickel on pumice.* Nickel nitrate (hexahydrate, 290 g.) was melted at 100°, granulated pumice (8—16 mesh, 150 g.) added, and stirring continued at 100° until the mass was granular. The temperature was very gradually raised at first. Reduction was carried out at 350°. This catalyst gave tetrahydrofuran between the temperature limits 200—400°. At 200° the consumption was only 18% and at 400° activity was rapidly lost. Catalysts (a), (b), and (c) were much improved by air oxidation at 550°, followed by reduction at 350°.

(d) *Nickel gauze.* Nickel gauze (28 mesh, 6 sq. ft., 620 g.) was fashioned into two compact rolls and fitted into a Pyrex tube of 26 mm. internal diameter. The length of the filling was 58 cm. A Pyrex thermometer pocket was fitted down the centre of the first roll of gauze. The nickel was quite inactive towards tetrahydrofurfuryl alcohol at 300°. Successive air oxidations at 550° followed by reduction produced the following amounts of water (c.c.) : 0·2, 0·2, 0·4, 0·8. Even then only very slight conversion of alcohol into tetrahydrofuran was observed. The nickel was therefore treated with chlorine at 550°, reduced, and then oxidised by air and reduced till no more hydrogen chloride was formed. Reduction gave 5 c.c. of water. A further chlorination raised this figure to 8·0 c.c. During use this figure varied by a few tenths of a c.c. and tended to rise slowly.

(e) *Nickel chromite on pumice.* Nickel chromite (63 g.; Adkins, Richards, and Davis, *J. Amer. Chem. Soc.*, 1941, **63**, 1320) was well mixed with moistened pumice (100 g.), and the mixture packed in the catalyst tube, heated, and reduced at 400°. Only about 0·8 c.c. of water was produced by oxidation and reduction.

(f) *Copper.* Three types were used. One was made by reduction of the oxide (B.D.H., *ex* wire) at 250° by hydrogen, another by reduction of copper nitrate on pumice; neither showed any activity. A third, copper chromite in pellet form, was reduced at 300°; in use at 365°, 95% of the alcohol input was consumed and a 41% yield of dihydropyran resulted.

(g) *Cobalt.* Cobalt nitrate (hexahydrate, 150 g., containing 0·11% of nickel) was heated with water (50 c.c.) and granulated pumice (150 g., 8—16 mesh) with stirring until granular. Reduction was carried out at 350—400°. The catalyst was inactive at 300°.

(h) *Iron.* Prepared in the usual way from granulated pumice and ferric nitrate (hexahydrate, 250 g.), the deposited oxide was difficult to reduce. After 12 hrs. at 550° in a stream of hydrogen, 13·5 c.c. of water were collected. The theoretical quantity for the reaction $Fe_2O_3 \longrightarrow 2Fe$ is 19 c.c., and for $Fe_2O_3 \longrightarrow Fe_3O_4$, 2 c.c. The catalyst was inactive at 400°.

(j) *Platinum.* Granulated pumice (60 g.) was treated with platinic chloride solution (19·5%, 55 c.c.) and reduced at 400°. The catalyst was rather ineffective at 300°.

(k) *Chromic oxide on alumina.* Active alumina (Grade A, British Aluminium Co., 4—6 mesh) was treated with a hot 25% solution of chromic oxide in water. After being heated and cooled twice, the alumina was dried. Its weight showed that about 7% of CrO_3 was present. The catalyst was finally heated in hydrogen at 400—450°. Passage of tetrahydrofurfuryl alcohol over this catalyst at 300° gave dihydropyran.

(l) *Raney alloy.* Granulated and sieved alloy (8—16 mesh, 460 g.) was packed into the Pyrex catalyst tube and treated at 450° with hydrogen chloride (15 l./hr.) for 5 hours. Aluminium chloride sublimed. The material was then removed from the tube, well mixed, and replaced. Oxidation of the catalyst with air at 550°, followed by reduction at 330°, gave 6·4 c.c. of water. The catalyst so prepared was very active, causing much decomposition to gaseous products at 270°. Active Raney catalyst suffered from the disadvantage of possessing considerable hold-up due to its porous nature.

(m) *Monel metal.* The alloy in the form of gauze (354 g., 60 mesh) was shown by analysis to contain: Cu, 30·0; Ni, 66·5; Fe, 1·2; Mn, 1·0%. It was clipped into pieces about 3 mm. square and packed into the catalyst tube around a central Pyrex thermometer pocket. Oxidation by air at 550°, followed by reduction, gave successively the following amounts of water: 1·5, 2·5, 3·1, 3·2, 3·3, 4·3 c.c. It was then used in the catalytic reaction.

(n) *"Ferry" alloy.* Alloy in the form of wire process scrap (241 g., about 30—36 S.W.G.) was shown to contain: Cu, 54·3; Ni, 43·9; Fe, 0·4; Mn, 1·1%. It was cut into small tufts and packed in the tube. Successive activations by oxidation and reduction gave 3·1, 3·9, 5·1, 5·6, 6·6, 8·4 c.c. of water. It is evident, therefore, by comparing these figures with those given above for Monel metal, that Ferry is the more easily oxidised alloy.

(o) *Cupronickel.* Bullet envelope cut-offs had the composition: Cu, 80·3; Ni, 19·7; Fe, 0·05%. The pieces (585 g.) were treated as before by oxidation and reduction and gave 1·3, 1·3, 3·1, and 4·0 c.c. of water. This catalyst was not very active, giving low consumption. It also deteriorated very rapidly.

(p) *"Permalloy."* The alloy contained Ni, 78·3; Fe, 21·4% and was in the form of thin strip. This (212 g.) was cut into small pieces and packed into the catalyst tube. Successive air oxidations, followed by reduction, at 500—530°, gave the following volumes of water: 0·5, 1·6, 2·2, 3·1, 3·8 c.c.; this depended on the temperature of reduction—*e.g.*, after the above series of activations a prolonged period of air oxidation at 580° gave only 1·2 c.c. of water by reduction at 330°, but much more water was then produced at 400—430° (3·1 c.c.), and no further reduction occurred until the temperature rose to 500—530°, whereat a further 1·5 c.c. were formed. It was concluded that reduction below 430° produced a mixture of nickel and iron oxide (probably Fe_3O_4), whereas only at the highest temperature was metallic iron formed. The high- and the low-temperature catalyst behaved differently in the reaction, as indicated in Table III; the latter was the more active, although less water had been evolved during its formation.

The crude tetrahydrofuran fraction (b. p. <160°) obtained from the low-temperature reduced catalyst contained 54% of di- and tetra-hydrofurans. The corresponding figure for the catalyst prepared by high-temperature reduction was 49%.

II. *Apparatus.*—The catalyst (100—150 c.c.) was contained in a Pyrex tube of 1 in. external diameter, resting inside an electric furnace inclined at 15° to the horizontal. The heated portion of the catalyst tube measured 24 ins., of which the middle 12 ins. were at a temperature constant to ± 5°. A series resistance enabled the temperature to be varied between 150° and 650°. Temperature was measured by a thermometer or thermocouple as described under catalyst (d). Tetrahydrofurfuryl alcohol was dripped on a strip of asbestos paper, along which it soaked gradually into the hotter part of the furnace. The exit end of the catalyst tube was connected to a suitable series of traps. The progress of a particular experiment, particularly in regard to catalyst activity, could be fairly well assessed by the size and luminosity of the flame obtained by igniting the issuing gases at a jet.

Reactivation was usually carried out by air oxidation at 550—580°, followed by reduction at 300—350°. It was also possible to reduce the nickel catalysts (c) and (d) after air oxidation by methanol at 370—380° or ethanol at 380—390°.

III. *Analysis of Products.*—The pyrolysate was divided into three fractions: (1) b. p. 50—160°, containing all the tetrahydrofuran; (2) b. p. 160—185°, consisting largely of unchanged alcohol; (3) residue. Fractionation through a 12" column packed with stainless steel rings was not sufficient to separate butaldehyde from tetrahydrofuran; about 2% remained. According to circumstances various methods were used to analyse the crude low-boiling fraction. Water was determined by either drying over a known weight of calcium chloride or freezing and filtering at − 78° through a pad of 90-mesh nickel gauze. *n*-Butaldehyde and 2 : 3-dihydrofuran were determined together by precipitation with aqueous dinitrophenylhydrazine. After potash treatment and distillation, which removed carbonyl compounds, dihydrofuran was determined alone as *γ-hydroxybutaldehyde-2 : 4-dinitrophenylhydrazone.* This formed golden laminæ, m. p. 116—117° (Found: C, 44·6; H, 4·7; N, 20·5. $C_{10}H_{12}O_5N_4$ requires C, 44·7; H, 4·5; N, 20·9%), from aqueous ethyl alcohol. Its solubility in water was 0·04% at 20°.

The higher-boiling material present in fraction (1) from a pure nickel catalyst contained methyl *n*-propyl ketone, b. p. 101—102°, identified and estimated as 2 : 4-dinitrophenylhydrazone. The only other substances present in any quantity were a liquid, b. p. 115—120°, which contained much butyl alcohol (identified as 3 : 5-dinitrobenzoate), and an unsaturated substance. The liquid (92 g.) was treated with excess of acetic anhydride at the b. p., a few drops of sulphuric acid being used as catalyst, and then saturated with bromine. The product was distilled, giving butyl acetate (93 g.), b. p. 124—127°, and a liquid (62 g.), probably a dibromobutyl acetate, b. p. 132—138°/16 mm.

Passage of the gaseous products not completely caught in Drikold traps through bromine gave a liquid, b. p. 142—144°/763 mm. (Found: C, 18·2; H, 3·0; Br, 77·75. Calc. for $C_3H_6Br_2$: C, 17·8; H, 3·0; Br, 79·2%), obviously propylene dibromide. After addition of bromine to the liquid, b. p. < 0°, from the pyrolysate, a substance, b. p. − 40° to − 30°, distilled off which was considered to be propane, since it was saturated and inflammable.

Fraction (3), the residue, b. p. > 185°, collected from many experiments, was washed with aqueous alkali and distilled. It contained 20% of tetrahydrofurfuryl alcohol and a substance, b. p. 100—101°/10 mm. (67% by wt.), believed to be *tetrahydrofuryl tetrahydrofurfuryl ether* (Found: C, 62·4; H, 9·0. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%). It was only very slightly soluble in water or aqueous alkali, but in the presence of 0·01N-mineral acid it rapidly dissolved without evolution of appreciable heat. The solution then gave the 2 : 4-dinitrophenylhydrazone of γ-hydroxybutaldehyde. A quantitative experiment, however, showed that the derivative was formed only to the extent of 79% of that expected from its proposed structure. Attempts at further purification by fractionation were of no avail, successive fractionations giving figures of 60 and 50%. A solution of the octahydro-ether (26 g.) in hydrochloric acid was treated with solid potassium carbonate, which caused the separation of an upper layer. This, which was completely miscible with water, was dried over potassium carbonate and distilled; two-thirds of it had b. p. 68—80°/14 mm., the remainder (7 g.) being mainly unchanged ether. The larger fraction was warmed to 80° with potassium hydroxide and distilled at 75°/12 mm. This product still gave a precipitate with dinitrophenylhydrazine, but treatment with 3 : 5-dinitrobenzoyl chloride in pyridine at 100° gave tetrahydrofurfuryl dinitrobenzoate which, after recrystallisation from petrol (b. p. 80—100°), had m. p. 83—84; it was identified by mixed m. p.

Fraction (3), from each vapour-phase experiment recorded in the tables, was treated with 4 vols. of 10% sodium hydroxide solution, which separated unchanged alcohol (soluble) from the octahydro-ether (insoluble). The amount of alcohol thus indicated was taken into account, along with that in fraction (2), when calculating consumption.

Fraction (2), bulked from many related experiments with a given catalyst, was distilled in a vacuum, and the proportion of tetrahydrofurfuryl alcohol in it ascertained. With the nickel catalysts (c) and (d) it contained 85—87% of pure unchanged alcohol, b. p. 66°/12 mm., together with 6% of the above octahydro-ether and 6% of b. p. < 66°/12 mm. The lowest-boiling fraction on redistillation had b. p. 120—150°/756 mm. and contained about 5% [*i.e.*, 0·3% on original fraction (2)] of *cyclo*pentanone, identified and estimated as dinitrophenylhydrazone.

IV. *Detection of Tetrahydrofurfuraldehyde.*—This aldehyde was first found in the recovered alcohol, fraction (2), from experiments with nickel under reduced pressure (see Table VI). The alcohol fraction, 15·2 c.c., was treated with aqueous 2 : 4-dinitrophenylhydrazine, and the precipitate recrystallised from ethyl acetate–ethyl alcohol (1 : 1). The hydrazone formed orange-yellow, prismatic needles, m. p. 130—131° (Found : C, 47·35; H, 4·55; N, 20·0. Calc. for $C_{11}H_{12}O_5N_4$: C, 47·2; H, 4·3; N, 20·0%). It did not depress the m. p. of an authentic specimen (see below).

The "Ferry" and "Permalloy" catalysts also produced small amounts of tetrahydrofurfuraldehyde. The recovered alcohol from experiments with Monel metal gave the dinitrophenylhydrazone of *cyclo*pentanone, which after one crystallisation from ethyl alcohol had m. p. 140—141°.

V. *Preparation of Tetrahydrofurfuraldehyde-2 : 4-dinitrophenylhydrazone.*—Repetition of the methods described in the literature for the preparation of the aldehyde did not give satisfactory results. Two other reactions, pyrolysis of the mixed barium salts of tetrahydrofuroic and formic acids, and Stephen's stannous chloride reduction of the nitrile, gave unexpected products. The former produced only tetrahydrofurfuryl alcohol (identified as 3 : 5-dinitrobenzoate) and the latter gave a small amount of δ-hydroxyvaleraldehyde. Finally, samples were successfully prepared in two ways, (i) lead tetra-acetate oxidation of the pinacol produced by catalytic reduction of furoin, and (ii) dehydrogenation of tetrahydrofurfuryl alcohol by means of a copper–chromium oxide catalyst.

(i) *Catalytic reduction of furoin.* Furoin was prepared as described by Buck and Ides (*J. Amer. Chem. Soc.*, 1932, **54**, 3302), although it was found better to distil the product (b. p. 158—162°/9 mm.) instead of recrystallising it. The ketol (125 g.) was reduced in methyl alcohol (375 g.) by means of Raney nickel (30 g.) and hydrogen (139 atm./18°). Rapid absorption occurred at 160—165° and ceased after 2·25 hrs. The pressure when cold was 84 atm. The product was separated into three fractions by distillation : (1) b. p. 122—146°/0·5 mm., 68 g.; (2) b. p. 160—180°/0·5 mm., 5 g.; (3) residue, 30 g. On treatment with cold water, fraction (1) largely dissolved, leaving an insoluble white substance (9·0 g.). This was non-ketonic and crystallised from hot water in prisms, m. p. 168—169°, which agrees with published data for the octahydroglycol (Kaufmann and Adams, *J. Amer. Chem. Soc.*, 1923, **45**, 3029) (Found : C, 59·5; H, 8·75. Calc. for $C_{10}H_{18}O_4$: C, 59·4; H, 8·9%). Fraction (2) was mixed with the water-soluble part of fraction (1) and redistilled, giving 54 g. of b. p. 125—130°/0·5 mm. On standing, this solidified, and a sample, after removal of contaminating oil by pressure, was recrystallised twice from petrol (b. p. 60—80°); it formed rosettes of needles, m. p. 80—81°, and was very soluble in all solvents. Analysis showed that it, too, was an octahydroglycol (Found : C, 58·85; H, 8·8%). It is probably identical with the second substance, m. p. 75°, isolated but not identified by Kaufmann and Adams.

Precipitation with aqueous dinitrophenylhydrazine showed that the low-melting glycol and the oil removed from it by pressure contained a carbonyl compound. The original crude, unpressed material, b. p. 125—130°/5 mm. (54 g.), was estimated to contain about 10% (5·5 g.) of carbonyl compound, possibly octahydrofuroin.

Oxidative fission of the tetrahydrofurfuraldehyde pinacols by lead tetra-acetate. The liquid glycol (13 g.), pressed from the low-melting solid (above), was treated in glacial acetic acid (25 c.c.) with lead tetra-acetate (24 g.; *Inorg. Syntheses*, 1939, **1**, 47). Excess of sulphuric acid was then added, and the mixture filtered. The resulting clear solution gave a positive test for furfuraldehyde (aniline acetate), and a scarlet dinitrophenylhydrazone. It would appear, therefore, that the crude glycol contained some furfuryl pinacol.

The low-melting glycol (not recrystallised, 2·02 g.) was dissolved in water (25 c.c.), and a solution of lead tetra-acetate (4·43 g.) in warm glacial acetic acid (30 c.c.) added with stirring. After 15 minutes, 5N-sulphuric acid (5 c.c.) was added, and the solution filtered. The clear filtrate gave a 2 : 4-dinitrophenylhydrazone which contained a small amount of the less soluble scarlet furfuryl compound. This was removed by crystallisation from ethyl acetate, and the remainder formed prisms, m. p. 128—130°, identical (mixed m. p.) with the hydrazone described in the next paragraph.

The recrystallised high-melting glycol (1·0 g.) and lead tetra-acetate (2·21 g.) in 15 g. of acetic acid gave a pure, homogeneous dinitrophenylhydrazone, which formed pale yellowish-brown prisms, m. p. 130—131°, from ethyl acetate, of the tetrahydrofurfuraldehyde derivative (Found : C, 47·4; H, 4·5; N, 20·0. Calc. for $C_{11}H_{12}O_5N_4$: C, 47·2; H, 4·3; N, 20·0%). Admixture with *cyclo*pentanonedinitrophenylhydrazone caused m. p. depression.

(ii) *Catalytic dehydrogenation of tetrahydrofurfuryl alcohol.* A catalyst similar to that described in B.P., 540,133, was prepared by mixing chromium nitrate (hydrate, 9 g.), copper nitrate (hexahydrate, 300 g.), copper oxide (25 g.), water glass (40 g.), copper carbonate (200 g.), and silica gel (60 g.) to a thick paste by warming; this was dried at 80° and fused in small portions before an air–gas blowpipe on an ordinary brick. The resulting material was broken up, packed in a furnace tube, and reduced at 300° in a stream of hydrogen. Tetrahydrofurfuryl alcohol was then passed over the catalyst at 300—350°. The product was distilled, giving about 12% of b. p. 60—170°. This fraction was accumulated from many experiments and redistilled after drying over sodium sulphate. There was no definite aldehyde fraction but the liquid of b. p. 140—160° gave tetrahydrofurfuraldehyde-2 : 4-dinitrophenylhydrazone which, after recrystallisation, had m. p. 130—131°.

In addition to the above, the 2 : 4-dinitrophenylhydrazones of the following carbonyl compounds were also prepared for reference purposes : γ-hydroxybutaldehyde, m. p. 116—117°; *δ-hydroxyvaleraldehyde*, m. p. 112—113° (Found : C, 47·1; H, 5·05; N, 19·75. $C_{11}H_{14}O_5N_4$ requires C, 46·8; H, 5·0; N, 19·9%); *n*-butaldehyde, m. p. 121—122°; methyl *n*-propyl ketone, m. p. 140—142°; *cyclo*pentanone, m. p. 140—141° (Found : C, 49·85; H, 4·55; N, 21·35. Calc. for $C_{11}H_{12}O_4N_4$: C, 49·9; H, 4·5; N, 21·2%).

VI. *Composition of Commercial Tetrahydrofurfuryl Alcohol.*—A large amount (2470 g.) of the alcohol was fractionated. More than 94·7% had b. p. 80—80·5°/19 mm. The higher-boiling residue amounted to 2·4%, and the fraction of b. p. 35—80°/19 mm to 2·5%. After drying, about a third of the latter had b. p. 118—121°. This gave *n*-butyl 3 : 5-dinitrobenzoate.

No trace of *cyclo*pentanol (b. p. 139—140°) could be found in the fractions from the commercial alcohol, nor was there any indication of furfuryl alcohol.

VII. *Behaviour of Tetrahydrofuran over the Gauze Catalyst* (d).—Tetrahydrofuran (41·5 c.c., 36 g., 0·5 g.-mol.) was passed over the reactivated catalyst during 1 hr. at 300—310°. The product (33 c.c.) consisted of 28 c.c., b. p. 57—67°, mostly tetrahydrofuran and free from *n*-butaldehyde or 2 : 3-dihydrofuran (dinitrophenylhydrazine), and 1·5 c.c. of b. p. < 0°. The latter was partly unsaturated towards bromine and gave 1 c.c. of water-insoluble dibromide, probably propylene dibromide. The rest was probably propane. The exit gases contained about one-third of their volume of carbon monoxide. Similar results were obtained at 280°, but less propylene was formed. Furan, b. p. 32—33°, could not be detected.

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17. *Reactions of Furan Compounds. Part IV. High-temperature Decomposition of the Vapours of Tetrahydrofuronitrile and Methyl Tetrahydrofuroate to give 2 : 3-Dihydrofuran and* cyclo*Propanealdehyde.*

By Christopher L. Wilson.

When the vapour of tetrahydrofuronitrile was passed over various dehydrating catalysts at temperatures between 300° and 400° it decomposed to give 2 : 3-dihydrofuran and hydrogen cyanide. Under similar conditions methyl tetrahydrofuroate also gave 2 : 3-dihydrofuran along with carbon monoxide and methyl alcohol. Above 400° both compounds gave *cyclo*propanealdehyde. The mechanism of the reactions is discussed.

During the preparation of tetrahydrofuronitrile by dehydration of the vapour of the corresponding amide by means of a silica gel or sodium phosphate catalyst at 300—400°, the formation of a small amount of a low-boiling liquid, shown to be largely 2 : 3-dihydrofuran, was observed. Experiments with the nitrile then demonstrated that heating splits it into dihydrofuran and hydrogen cyanide.

Methyl tetrahydrofuroate under similar conditions also decomposed to give 2 : 3-dihydrofuran; in this case the other fragments were carbon monoxide and methyl alcohol: $C_4H_7O\cdot CO_2Me = C_4H_6O + CO + MeOH$.

With both tetrahydrofuronitrile and the ester a new substance appeared in the reaction product as the temperature was raised above 400°. This was a carbonyl compound and analysis of the well-defined *p*-nitro- and 2 : 4-dinitro-phenylhydrazones showed that it was C_4H_6O. Only five isomers of this composition are known and, as the m. p.'s in the following table indicate, identity with either (*a*) (crotonaldehyde) or (*c*) (α-methacraldehyde) would appear to be out of the question.

The product from the ester contained the free carbonyl compound, in contrast to that from the nitrile which contained the cyanohydrin. It had a pungent odour, suggesting (*b*) (methyl vinyl ketone), but a mixed m. p. of the phenylhydrazones showed non-identity. The evidence of odour was then shown to be misleading, since attempted catalytic reduction removed the pungency without affecting the carbonyl constituent. This definitely ruled out (*a*), (*b*), and (*c*) which are not only very pungent but also possess reducible carbon double bonds. The balance of evidence was, therefore, in favour of (*e*), *cyclo*propanealdehyde.

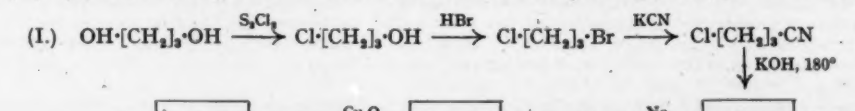
Carbonyl compounds, C_4H_6O.

Compound.	B. p.	Melting point of— Oxime.	Phenylhydrazone.	*p*-Nitrophenylhydrazone.	2 : 4-Dinitrophenylhydrazone.	Dimedon compound.
(*a*) CHMe:CH·CHO	104°	119°	56°	184—185°	—	—
(*b*) CH_2:CH·CO·Me	80	—	74—75 [1]	—	—	—
(*c*) CH_2:CMe·CHO [2]	69	—	73—74 [1]	161—163	206—206·5°	—
(*d*) $CH_2\cdot CH_2\cdot CH_2\cdot CO$	(96)	—	95—96	—	—	—
(*e*) $CH_2\cdot CH_2\cdot CH\cdot CHO$ [3]	(100)	86	67	—	—	168°
(*f*) Reaction product	80—100 [4]	—	67—68 [4]	131—133 [4, 5]	172—175 [4, 5]	162 [4]

[1] Pyrazolines. [2] Shriner and Sharp, *J. Amer. Chem. Soc.*, 1940, **62**, 2245. [3] Shuikina, *Chem. Zentr.*, 1937, II, 3152; *J. Gen. Chem. Russ.*, 1937, **7**, 983. [4] From methyl tetrahydrofuroate. [5] From tetrahydrofuronitrile.

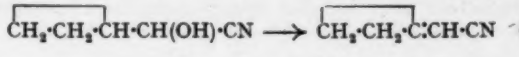
Unexpected confirmation was provided by the unusual behaviour of the phenylhydrazone. After standing for a few hours in air, this white crystalline substance decomposed into a brown liquid exactly as Shuikina (*loc. cit.*) found for *cyclo*propanealdehydephenylhydrazone.

Final proof of identity depended on comparison with authentic material. Shuikina (*loc. cit.*) synthesised his aldehyde (II) by the following series of reactions from trimethylene glycol (I). In the present work this



synthesis was followed except that the last two steps were replaced by stannous chloride reduction of the nitrile according to Stephen. The overall yield of aldehyde was small, but sufficient was obtained to show identity by mixed m. p. of the *p*-nitro- and the 2 : 4-dinitro-phenylhydrazone.

Over a silica gel catalyst above 500° the nitrile gave only traces of (II), the chief product being a liquid, b. p. 130—140°. This had an empirical formula C_5H_5N, was non-basic, and had an odour reminiscent of an aliphatic nitrile. A similar substance was also obtained during the dehydration of ammonium tetrahydrofuroate under the same conditions. Since the experiments at lower temperatures indicated the formation of the cyanohydrin of (II), it is probable that the oxygen-free compound, C_5H_5N, had the structure (III):



(III.)

The possibility that the *cyclo*propane ring had opened under the drastic conditions of reaction cannot be ruled out: further experiments are necessary to settle this question.

In the experiments with the nitrile it was noticed that, as the temperature approached 400°, the amount of 2 : 3-dihydrofuran increased; thereafter up to 500° it decreased and the aldehyde (II) appeared in increasing quantities. It is, therefore, not illogical to suppose that the aldehyde was a rearrangement product of the furan; the molecules are, of course, isomeric. There is support for this hypothesis if 2 : 3-dihydrofuran can behave, as its structure would suggest, like a vinyl ether. Some vinyl ethers are known to rearrange to carbonyl compounds on heating. For example, Claisen (*Ber.*, 1896, **29**, 2931) showed that α-methoxystyrene (IV) was converted into propiophenone (V). In this example an alkyl group migrates from oxygen to carbon.

$$\text{(IV.)}\quad \text{Ph·C(OMe):CH}_2 \longrightarrow \text{Ph·CO·CH}_2\text{·CH}_3 \quad \text{(V.)}$$

In dihydrofuran a similar migration would mean shrinkage of the ring from five to three members:

These reactions will be studied further.

Experimental.

I. *Apparatus.*—The arrangement of the furnace and catalyst tube was as described in the preceding paper.

II. *Preparation of Catalysts.*—(a) *Silica gel.* Commercial silica gel was prepared as described on p. 55

(b) *Alumina on pumice.* Granulated pumice (8—16 mesh) was impregnated with aqueous (40%) aluminium nitrate, dried at 80°, and then heated slowly to 400° in a stream of air in the catalyst tube.

(c) *Calcium phosphate.* Calcium phosphate, ammonium phosphate, and graphite were mixed with water, heated to dryness, and the cake broken and packed in the catalyst tube. The catalyst was heated in nitrogen at 385° before use (cf. B.P., 317,500).

(d) *Sodium phosphate.* Pumice (8—16 mesh) was impregnated with a hot solution of sodium dihydrogen phosphate (120 g.) and phosphoric acid (glacial, 15 c.c.) in water (85 c.c.), and dried by raising the temperature slowly to 300° in a stream of air (cf. B.P., 506,038).

In some experiments the catalyst tube was filled with earthenware rings to try the effect of a relatively inert material with little, if any, catalytic properties.

III. *Preparation of Materials.—Furoic acid.* Furfuraldehyde (technical, 768 g., 8 g.-mols.) was treated with sodium hydroxide as described in *Organic Syntheses* (Coll. Vol. I, p. 270). The yield of the acid in different experiments varied between 280 and 340 g. (63—73%), m. p. 130—131°. Some furfuraldehyde was recovered from the ethereal extract by distilling it at 165—171°, and extracting the aldehyde from the distillate (furfuryl alcohol) by shaking it with aqueous sodium hydrogen sulphite.

Furoyl chloride, b. p. 174°, was prepared in 95% yield by the action of thionyl chloride on the acid. Reaction with aqueous ammonia gave the amide, m. p. 138—140°, b. p. 145—148°/11 mm. Methyl furoate, b. p. 178—180°, resulted in 70% yield either by reaction of the chloride with methyl alcohol or by direct esterification of the acid.

Tetrahydrofuroic acid (cf. Weinhaus and Sorge, *Ber.*, 1913, **46**, 1929). Furoic acid (m. p. 130—131°; 200 g.), dissolved in ammonia (*d* 0·880; 150 c.c.) and water (350 c.c.), was introduced into a rotating Bergius converter (capacity 2 l.) along with Raney nickel (20 g.) and hydrogen (93 atm./20°). Reduction was complete in 5 hrs. at 130—150°. A weighed sample of the resulting solution after filtration from catalyst was boiled with excess of standard alkali and back-titrated with acid (phenolphthalein as indicator). This showed that recovery of organic acid was about 94%. Acidification showed the absence of more than 5% of unreduced furoic acid. Tetrahydrofuroic acid was isolated in 60% yield by strongly acidifying the solution of the ammonium salt and repeatedly extracting it with ether. A better yield (90%) was obtained by distilling the methyl ester with an equal volume of 2N-hydrochloric acid until methyl alcohol ceased to be evolved. The residue was then distilled in a vacuum; b. p. 118—120°/18 mm.

Methyl tetrahydrofuroate. Reduction of a methyl-alcoholic solution of methyl furoate with a Raney nickel catalyst (nickel on kieselguhr was less effective) took 5 hrs. at 120°. The product, 90% yield, b. p. 77—78°/15 mm., was completely miscible with cold water.

Tetrahydrofuroamide. A solution of ammonium tetrahydrofuroate was evaporated to dryness in a vacuum, and the residue heated to 220—230° in a stream of ammonia so that water could distil off. The residue was then distilled, b. p. 134—136°/10 mm.; yield 76%. The aqueous distillate from the ammonia treatment was distilled separately to give a further 5% yield of the amide.

Under these conditions of amide formation, ammonium furoate gave a product (probably a complex of acid and amide), b. p. 160°/11 mm. The ammonia treatment thus served to separate any remaining unreduced furoic acid.

Tetrahydrofuronitrile. Attempts to dehydrate the amide by carbonyl chloride at high temperatures failed. Smooth dehydration to the nitrile was, however, effected by passing the vapour of the amide over a silica gel or sodium phosphate catalyst. The amide was contained in a specially designed dropping-funnel and was kept liquid by wrapping the funnel with lead tubing carrying steam. Instead of a tap, the funnel had an internal valve made by grinding a tapered glass rod to fit the exit neck of the funnel. The rod extended through a rubber gasket in the upper neck of the funnel. In this way the use of tap lubricant was obviated.

Dehydration of amide. (*a*) Over silica gel. An amide input of 10 g./hr. and nitrogen carrier (2 l./hr.) gave at 360—400° a product consisting of nitrile and 2 : 3-dihydrofuran, identified by conversion into γ-hydroxybutaldehyde-2 : 4-dinitrophenylhydrazone (see previous paper), together with some hydrogen cyanide. The catalyst deteriorated in use but was readily reactivated by treatment with a stream of air at 550—580°.

As the temperature was reduced below 330° the consumption of amide and the amount of dihydrofuran produced both decreased. After allowance for recovered amide, the yield of nitrile and consumption at various temperatures were as follows, a freshly reactivated catalyst being used for each experiment: 290°, 74%, 60%; 310°, 55%, 80%; 330°, 40%, 90%. At the highest temperature in this series (330°) about 8% of the total product consisted of a mixture, b. p. 50—62°, of di- and tetra-hydrofuran containing 55% of the former.

(*b*) Over sodium phosphate. This catalyst at 400° gave a 90% yield of pure nitrile with an amide consumption of 50—85%.

Tetrahydrofuronitrile was a colourless, mobile liquid, immiscible with water; b. p. 71—73°/10 mm. (Found: C, 61·7; H, 7·3; N, 14·4. Calc. for C_5H_7ON: C, 61·9; H, 7·3; N, 14·4%). The only other preparation recorded is that of Williams (*Ber.*, 1927, **60**, 2509), who dehydrated the oxime with acetic anhydride.

IV. *Reactions of Tetrahydrofuronitrile Vapour over Various Catalysts.*—(a) *Earthenware rings.* With nitrogen (2 l./hr.) as carrier gas, 70% of the nitrile was recovered at 450°. About 10% of the product consisted of impure 2 : 3-dihydrofuran.

(b) *Silica gel.* At 500° the nitrile gave a product containing about 10% of b. p. 130—140°, 20% of 2 : 3-dihydrofuran–tetrahydrofuran mixture (48% of former), and 10% of unchanged nitrile. The fraction, b. p. 130—140°, had a sweet odour reminiscent of an aliphatic nitrile (Found: C, 74·75; H, 8·15; N, 14·3. Calc. for C_5H_5N: C, 75·9; H, 6·3; N, 17·7%). It was colourless when freshly distilled. A similar liquid was obtained in experiments with ammonium tetrahydrofuroate (see below).

(c) *Sodium phosphate.* Little reaction was evident below 450°. At this temperature about 10% of the nitrile reacted to give mainly hydrogenated furans. At 500° the reaction product contained hydrogen cyanide, only a little hydrogenated furans, and mainly a liquid, b. p. 42—44°/14 mm., which gave a copious precipitate of Prussian-blue on treatment with sodium hydroxide and ferrous sulphate, followed by heating and acidification. The liquid seemed to be a cyanohydrin, since reaction with 2 : 4-dinitrophenylhydrazine dissolved in 2N-hydrochloric acid gave a precipitate which crystallised from ethyl acetate–ethyl alcohol in orange-red prisms, m. p. 173—175° (Found: C, 48·0; H, 4·2; N, 22·2. $C_{10}H_{10}O_4N_4$ requires C, 48·0; H, 4·0; N, 22·4%). This was shown to be cyclo*propanealdehyde*-2 : 4-*dinitrophenylhydrazone* by mixed m. p. with an authentic specimen, m. p. 172—174°, synthesised as described below. The p-*nitrophenylhydrazone* crystallised from ethyl alcohol in brown needles, m. p. 126—127° (Found: C, 59·1; H, 5·2; N, 20·2. $C_{10}H_{11}O_2N_3$ requires C, 58·5; H, 5·4; N, 20·5%), undepressed on admixture with an authentic specimen (m. p. 126—127°).

Identification of 2 : 3-*Dihydrofuran.*—The low-boiling fractions from the above experiments were collected, dried over potassium hydroxide, and distilled. The fraction, b. p. 53—58° (Found: C, 69·2; H, 8·95. C_4H_6O requires C, 68·6; H, 8·6%), reacted rapidly with bromine in aqueous acetic acid solution and dissolved with heat evolution on treatment with 0·1N-sulphuric acid. This solution with 2 : 4-dinitrophenylhydrazine hydrochloride solution gave a golden-yellow crystalline hydrazone, m. p. 114—115°, shown by mixed m. p. to be derived from γ-hydroxybutaldehyde (cf. p. 56). Quantitative precipitation showed that the liquid, b. p. 53—58°, contained about 50% of 2 : 3-dihydrofuran. The remainder was probably tetrahydrofuran.

V. *Catalytic Dehydration of Ammonium Tetrahydrofuroate.*—An aqueous solution (50%) of ammonium tetrahydrofuroate containing excess of ammonia was introduced into the catalyst chamber at a rate of 10 c.c./hr. Ammonia (2 l./hr.) was also admitted as carrier.

(a) *Over earthenware rings.* At 500° a product was obtained which behaved like an equimolecular mixture of tetrahydrofuroic acid and amide. The crude material was analysed [Found: C, 50·15; H, 7·2; N, 5·4; *M* (cryoscopic in benzene), 155; equiv. by titration, 295. Calc. for $(C_4H_7O)\cdot CO_2H$, $(C_4H_7O)\cdot CO\cdot NH_2$: C, 51·9; H, 7·4; N, 6·1%; *M*, 231].

(b) *Over silica gel.* At 400° the results were like those with earthenware rings at 500°. At 500—600°, however, the product contained a water-insoluble liquid, b. p. 130—140°/760 mm., similar to that (C_5H_5N) obtained by passage of tetrahydrofuronitrile vapour over silica gel (Section IV). Higher-boiling fractions of the reaction product, b. p. 70—75°/16 mm. [Found: C, 61·55; H, 7·05; N, 9·0; *M* (cryoscopic in benzene), 80 approx. Calc. for C_5H_7ON: C, 61·9; H, 7·3; N, 14·4%; *M*, 97], appeared to consist largely of tetrahydrofuronitrile.

VI. *Reactions of Methyl Tetrahydrofuroate Vapour.*—The ester was passed into the catalyst chamber at a rate of 20 g./hr.

(a) *Over sodium phosphate.* Between 10 and 50% of the ester was consumed at temperatures between 450° and 550°. Variation of conditions, temperature, and carrier gas (nitrogen, carbon dioxide) appeared to have but little influence on the result. There were indications, however, that a fresh catalyst gave a higher consumption. Carbon monoxide was identified in the issuing gases. The reaction product (20—30% yield by weight, after allowance for recovered ester) had b. p. 45—90°. A sample (10·8 c.c.) of this liquid was distilled and divided into four fractions. One fraction, b. p. 55—65° (1·8 c.c.) gave methyl 3 : 5-dinitrobenzoate, m. p. 106—107° (and mixed m. p.), on treatment with dinitrobenzoyl chloride in pyridine. Another fraction, b. p. 75—90° (2·3 c.c.), was treated with aqueous dinitrophenylhydrazine and the precipitate recrystallised from ethyl acetate; it formed orange-red prisms, m. p. 172—175° (Found: C, 47·9; H, 4·0; N, 22·1%), identified as the derivative of (II) by mixed m. p. The amount of derivative indicated that about half the fraction was this aldehyde. The yield on consumed ester, therefore, was 2—3%.

The fraction, b. p. 45—55° (4·3 c.c.), after being shaken with aqueous bisulphite, was shown to contain 2 : 3-dihydrofuran by preparation of γ-hydroxybutaldehyde-2 : 4-dinitrophenylhydrazone, m. p. 116—118° (Found: C, 44·3; H, 4·3; N, 20·4. Calc. for $C_{10}H_{12}O_5N_4$: C, 44·7; H, 4·5; N, 20·9%). The remaining fraction, b. p. 65—75° (2·0 c.c.), had, like the others, a pungent smell recalling crotonaldehyde. It was treated with hydrogen in the presence of Adams's platinum catalyst. Only 85 c.c. were absorbed but the pungent odour had disappeared. Brady's reagent then precipitated the 2 : 4-dinitrophenylhydrazone of (II), m. p. 164—172°, identified by mixed m. p. The *p*-nitrophenylhydrazone had m. p. 126—133°. The dimedon derivative, m. p. 160—162°, was also prepared by precipitation from methyl-alcoholic solution (Found: C, 72·15; H, 8·8. Calc. for $C_{20}H_{28}O_4$: C, 72·3; H, 8·4%).

In another series of experiments the product, b. p. <100°, was treated with phenylhydrazine. Heat was evolved and water separated. Distillation gave the phenylhydrazone of (II), b. p. 140—150°/17 mm., white needles from ethyl alcohol, m. p. 68—69° (Found: C, 75·3; H, 7·3; N, 17·45. Calc. for $C_{10}H_{12}N_2$: C, 75·0; H, 7·6; N, 17·5%). It decomposed to a brown oil on standing for a few hours in air; analysis of the decomposition product showed that oxygen had been absorbed and nitrogen evolved (Found: C, 71·3; H, 6·75; N, 12·55%). The phenylhydrazone did not give a violet colour with ferric chloride solution, thus differentiating it from the phenylmethylpyrazoline from methyl vinyl ketone (see below).

In some of the pyrolyses butadiene was shown to be present by preparation of the tetrabromide.

(b) *Over alumina on pumice.* The results were similar to those with sodium phosphate.

(c) *Over silica gel.* At 325—350°, 65% of the ester was recovered unchanged. A little mixed hydrogenated furans were present. At 375°, 80% of the ester was consumed and a 30% yield (wt.) of product, b. p. <100°, was obtained. This contained 2 : 3-dihydrofuran and an aldehyde extracted by bisulphite solution. The solution gave a 2 : 4-dinitrophenylhydrazone, which crystallised from ethyl alcohol in orange-brown needles, m. p. 120—125° (Found: C, 47·7; H, 4·8; N, 22·25. Calc. for $C_{10}H_{12}O_4N_4$: C, 47·6; H, 4·8; N, 22·2%), showing (mixed m. p.) that the aldehyde was *n*-butaldehyde.

At 400°, with carbon dioxide as carrier gas, the ester gave a 35% yield (wt.) of liquid, b. p. <100°, and no unchanged ester. This contained some 2 : 3-dihydrofuran and about a third of its weight of the aldehyde (II), extracted by bisulphite. The dinitrophenylhydrazone had m. p. 169—174° after crystallisation from ethyl acetate.

(d) *Over calcium phosphate.* This catalyst was less effective than sodium phosphate but gave the same type of result.

(e) *Over marble chips.* With these in the catalyst tube, the only recognisable products at 450—475° were unchanged ester, methyl alcohol, and tetrahydrofuran.

VII. *Synthesis of Authentic* cyclo*Propanealdehyde.*—cyclo*Propyl cyanide* (Henry, *Rec. Trav. chim.*, 1899, **18**, 228; Dalle, *ibid.*, 1902, **21**, 123; Demjanov and Fortunatov, *Ber.*, 1907, **40**, 4307; Demjanov and Dojarenko, *Ber.*, 1908, **41**, 43). γ-Chlorobutyronitrile (141 g.) was added slowly to potassium hydroxide pellets (200 g.) contained in a flask immersed in an oil-bath at 190°. The distillate was collected and extracted with ether, the extract dried over potassium carbonate, and distilled, giving 29 g. (33%) of the cyclic cyanide, b. p. 132—134°. During the reaction much ammonia was evolved. The flask residue was dissolved in water and acidified (Congo-red), and the solution repeatedly extracted with ether; distillation gave *cyclo*propanecarboxylic acid, 25 g., b. p. 180—184°.

cyclo*Propanealdehyde.* Stannous chloride was dried by heating in a vacuum to 200° and then suspended in ether (500 c.c.) which had previously been dried over phosphoric oxide and distilled. Hydrogen chloride was then introduced until two layers were formed (cf. Stephen, J., 1925, **127**, 1874). *cyclo*Propyl cyanide (27 g.) was added, and the mixture well shaken at intervals during 3 hours. Water was added, the ether removed, and the residue distilled in steam. The distillate consisted of ether, water, unreacted nitrile, and some aldehyde, not isolated, but indicated by preparation of derivatives to be 5·5 g. (20%). The 2 : 4-dinitrophenylhydrazone separated from ethyl acetate in orange-red prisms, m. p. 168—172° (Found: C, 47·2; H, 4·3; N, 21·3. Calc. for $C_{10}H_{10}O_4N_4$: C, 48·0; H, 4·0; N, 22·4%). The *p*-nitrophenylhydrazone crystallised from ethyl alcohol in golden-brown prisms, m. p. 129—132° (Found: C, 58·7; H, 5·3; N, 20·3. Calc. for $C_{10}H_{11}N_3O_2$: C, 58·5; H, 5·4; N, 20·5%). These two derivatives were used for the mixed m. p.'s already referred to.

VIII. *Methyl Vinyl Ketone.*—Derivatives of this ketone were made for reference purposes. 4-Hydroxybutan-2-one (Wohl and Prill, *Annalen*, 1924, **44**, 139; D.R.-P., 223,207; Friedländer, Vol. 10, p. 1007) was prepared by keeping a mixture of acetone (300 g.), formalin (35%, 100 g.), and sodium hydroxide (0·5N, 10 c.c.) for one hour below 30°. After neutralisation, the liquid was distilled, giving the ketone, 30 g., b. p. 90—100°/17 mm. Repetition of the example described in the patent gave from 1 kg. of acetone, 75 g. of hydroxy-ketone, b. p. 75—100°/17 mm. The acetyl derivative, b. p. 90—100°/17 mm., prepared by reaction with boiling acetic anhydride in presence of zinc chloride, was pyrolysed by passage through a Pyrex tube filled with earthenware rings at 450°. The resulting ketone, b. p. 77—80°, 60% yield, did not give a homogeneous 2 : 4-dinitrophenylhydrazone or *p*-nitrophenylhydrazone but with phenylhydrazine produced 1-phenyl-3-methylpyrazoline, b. p. 170—180°/17 mm., pale brown prisms, m. p. 71—74°, from ethyl alcohol (Found: C, 74·6; H, 7·2; N, 17·6. Calc. for $C_{10}H_{12}N_2$: C, 75·0; H, 7·6; N, 17·5%). This gave an intense violet coloration with acidified ferric chloride solution. The substance depressed the m. p. of the phenylhydrazone of (II) to 45—55°.

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18. *Reactions of Furan Compounds. Part V. Formation of Furan from Furfuraldehyde by the Action of Nickel or Cobalt Catalysts: Importance of Added Hydrogen.*

By CHRISTOPHER L. WILSON.

Above 200° furfuraldehyde vapour was decomposed into furan and carbon monoxide on contact with a catalyst containing nickel or cobalt. Under favourable conditions the yield of furan attained 65%. Sufficient hydrogen had to be added along with the furfuraldehyde to obtain high conversion and prevent rapid deterioration of the catalysts.

Small amounts of methylfuran and *n*-butaldehyde accompany the furan.

THE same kind of catalysts which were effective in eliminating the side chain of tetrahydrofurfuryl alcohol (Part III, this vol., p. 52) have now been shown to decompose furfuraldehyde into furan and carbon monoxide. Perhaps the most interesting feature of the reaction was that hydrogen had to be added along with the furfuraldehyde, otherwise the conversion was very small and the catalyst deteriorated extremely rapidly.

Loss of the side chain of the aldehyde was not entirely unexpected, since catalysts such as nickel, cobalt, and platinum are known (cf. Hurd, "Pyrolysis of Carbon Compounds," p. 240) to bring about elimination of carbon monoxide from aldehydes, and furfuraldehyde itself, when reduced as a vapour over a Sabatier–Senderens nickel catalyst at 270°, afforded a small amount of what was assumed to be furan (Padoa and Ponti, *Gazzetta*, 1907, **37**, 105). These experiments were repeated by Pringsheim and Noth * (*Ber.*, 1920, **53**, 114), who identified furan; although they did not record the yield, it is evident that this could not possibly have been greater than 50% and was probably very much less.

The beneficial effect of hydrogen in decarbonylation was unexpected. The only other observation of a like nature is that of Wojcik and Adkins (*J. Amer. Chem. Soc.*, 1933, **55**, 1293), who found that the presence of hydrogen enhanced the elimination by nickel of the primary aliphatic alcohol group in the liquid phase. In this reaction the aldehyde is almost certainly an intermediate. With furfuraldehyde the effect of hydrogen was most pronounced; *e.g.*, with nickel at 280° the consumption of aldehyde fell from 86 to 9% when hydrogen was replaced by carbon dioxide or nitrogen. Restoration of the hydrogen supply raised consumption again but only to 43%, indicating that irreparable deterioration had occurred.

Catalytic Effect of Different Metals.—Catalysts containing nickel or cobalt gave rise to furan accompanied by a minor proportion of methylfuran. Iron and copper chromite catalysts gave only methylfuran, and metallic copper deposited on pumice was inactive. Results for different catalysts are collected in Table I. The figures for consumption have but little absolute meaning since they depend on many factors, including

* These authors' use of an iron reaction tube to hold the catalyst has been misunderstood (cf. Kaufmann and Adams, *J. Amer. Chem. Soc.*, 1923, **45**, 3029) to imply the use of an *iron* catalyst.

the amount of active catalyst present. The preparation and activation of each of the catalysts was described in Part III.

TABLE I.

Conversion of Furfuraldehyde into Furan and Methylfuran by Means of Various Catalysts.

(Temp. 280—290°. Input: aldehyde, 1·0 g.-mol./hr.; each expt., 0·5 g.-mol.; hydrogen, 15 l./hr.).

Catalyst.	Consumption of aldehyde, %.[1]	Yield of furan, %.[1]	Yield of methylfuran, %.[1]
Ni gauze	66	53	8
Ni on pumice	75	42	14
Ni chromite	30	33	10
Raney alloy (Ni,Al)	77	33	8·5
Monel metal (Ni,Cu)	69	65	2
Ferry alloy (Ni,Cu)	66	63	6
Cupronickel (80 : 20)	40	48	2
Permalloy: (*a*) Ni–Fe oxide [3]	55	46	11
(*b*) Ni–Fe.[4]	37	45	12
Co on pumice	42	21	18
Fe on pumice	21	0	18
Cu chromite [2]	65	0	80

[1] "Consumption" and "yield" have the significance assigned to them in Part III.
[2] In this experiment hydrogen input was increased to 45 l./hr.
[3] Catalyst produced by reduction of the oxidised alloy below 400°.
[4] Catalyst produced by reduction of the oxidised alloy at 550°.

The most satisfactory catalyst, combining fair yield of furan with long active life, was nickel gauze. All the others deteriorated much more rapidly. However, the small proportion of methylfuran in the product from Monel metal and cupronickel is noteworthy.

Two other substances were identified in the reaction product, *viz.*, propylene in the exit gases and *n*-butaldehyde in the methylfuran fraction. The amount of aldehyde produced varied with the catalyst: the yield from nickel gauze was 1·4%, from Raney, Ferry, and Monel alloys 2·8, 2·3, and 2·6%, respectively, and from the two Permalloy catalysts about 6%. These two substances probably arise by ring fission of furan, but confirmation is lacking.

Effect of Temperature and Pressure.—As the temperature of the catalyst was raised from 200° to 300°, consumption of aldehyde increased from about 10 to almost 100%, whereas yield of furan usually fell by 10—14 units % over this range. The majority of the catalysts operated satisfactorily between 270° and 290°; a temperature in this range usually combined good yield with high consumption. Data illustrating the effect of variation of temperature with a nickel catalyst are given in Table II. The slight deterioration of this catalyst is evident by comparison of expts. 1 and 8. Other catalysts behaved much the same except that deterioration was more pronounced.

TABLE II.

Furan from Furfuraldehyde at Various Temperatures with a Nickel Gauze Catalyst.

(Input: Aldehyde, 1·0 g.-mol./hr.; each expt., 0·5 g.-mol. Hydrogen, 15 l./hr. Consecutive experiments without reactivation.)

Temp.	300°	250°	230°	200°	280°	280°	280°	300°	320°	350°	400°
Consumption of $C_4H_3O\cdot CHO$, %	99	52	38	14	65	66	61	73	69	57	99
Yield of furan, %	42	57	61	56	51	53	55	47	42	38	2

Reduction of pressure from atmospheric to about 200 mm. caused a diminution of consumption at 280° from 65 to 26%. The yield of furan (70%) seemed appreciably higher, however, and no methylfuran could be isolated. The alloy catalysts were almost completely inactive at low pressures.

Variation of Input Rates.—With constant aldehyde input, increase in added hydrogen improved consumption but did not appreciably affect yield. At high rates of flow, yield fell slightly owing to incomplete trapping of the products. Data illustrating this are contained in Table III.

TABLE III.

Furan from Furfuraldehyde with a Nickel Gauze Catalyst: Effect of Variation of Hydrogen Input.

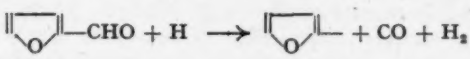
(Temp. 280°. Aldehyde input, 1·0 g.-mol./hr.; each expt., 0·5 g.-mol.)

Hydrogen input, l./hr.	3	15	40	75
Consumption of aldehyde, %	23	47	62	69
Yield of furan, %	53	57	53	48

The desirability of a high ratio of hydrogen to aldehyde for good consumption was confirmed by experiments with different aldehyde input rates, the hydrogen flow being kept constant at 15 l./hr. Increase of aldehyde input from 0·5 to 1·0 and then 3·0 g.-mols./hr. lowered consumption from 87 to 66 and then to 38%. The yield of furan remained effectively constant at 51—53%.

Mechanism.—Since the added hydrogen, apart from the small amount used in the formation of methylfuran, issued from the catalyst tube unchanged, its effect was purely catalytic. Two explanations of this appear possible. Hydrogen either functions by keeping the active centres on the catalyst clean by washing away poisons, or it takes a direct part in the elimination. The first view is supported by the fact that elimination occurred, although only to a very limited extent, even in the absence of added hydrogen (cf. also Hurd, Goldsby, and Osborne, *J. Amer. Chem. Soc.*, 1932, **54**, 2553). Moreover, the catalyst failed to regain completely its original activity when the hydrogen was restored.

Unlike hydrogen, nitrogen or carbon dioxide did not promote the elimination. Hydrogen may, therefore, be an essential reaction partner but it is not easy to suggest how this happens. It may be that collision between a hydrogen atom and the aldehyde affords a hydrogen molecule, carbon monoxide, and a furyl radical in a



manner somewhat analogous to the recombination of two hydrogen atoms in the presence of a third body to dissipate the excess energy. The furyl radical subsequently acquires a further hydrogen atom. Although the concentration of hydrogen atoms in the free space under the conditions of the present experiments would appear to be vanishingly small, it may be that reactions of this type do occur on the surface of the catalyst.

Finally, it should be noted that the catalytic reaction described supersedes older methods for preparing furan (cf. *Org. Synth.*, Coll. Vol. I, p. 269; Wagner and Simons, *J. Chem. Educ.*, 1936, **13**, 265; Hurd, Goldsby, and Osborne, *loc. cit.*).

Experimental.

The technique was as described in previous parts of this series.

Catalysts.—The preparation, activation, and reactivation of the catalysts were described in Part III (*loc. cit.*), but an additional one, pure cobalt on pumice, was prepared as follows. Cobalt nitrate ("AnalaR," hexahydrate, 150 g.) containing less than 0·002% of nickel was heated to 100°, and granulated pumice (8—16 mesh, 100 g.) added. Heating was continued until the mass was dry and granular, and it was then reduced in the catalyst tube at 350—380°. This catalyst behaved exactly like that (*loc. cit.*) containing 0·11% of nickel.

Analysis of Products.—Propylene was shown to be present in the gaseous products by formation of the dibromide. The liquid product caught in the traps was distilled from a Claisen flask embodying a 10" column. Furan (70—80%), methylfuran, and *n*-butaldehyde were contained in the fraction, b. p. < 150°. Unreacted aldehyde distilled between 150° and 170°, and a small residue remained in which furfuraldehyde was estimated by the contraction on shaking with aqueous bisulphite.

The fraction, b. p. <150°, was dried over calcium chloride and distilled through a short column to separate furan, b. p. 30—33·5°, identified if necessary by preparation of the maleic anhydride adduct, m. p. 104—105° (decomp.) (Diels and Alder, *Ber.*, 1929, **62**, 554). The last traces of aldehyde and water were best removed by standing over potassium or sodium hydroxide and distillation. Methylfuran and *n*-butaldehyde distilled together between 60° and 75°. They were separated by aqueous bisulphite. The aldehyde was identified as the 2 : 4-dinitrophenylhydrazone, orange needles from ethyl alcohol, m. p. 121—123°, not depressed by admixture with an authentic specimen; the absence of other carbonyl compounds in this fraction was indicated by the homogeneity of the dinitrophenylhydrazone. Methylfuran after drying over sodium hydroxide had b. p. 63—65° (Found : C, 73·0; H, 7·05. Calc. for C_5H_6O : C, 73·2; H, 7·3%) and was readily distinguished from tetrahydrofuran, b. p. 64—66°, by either the rapid darkening and resinification on addition of a drop of concentrated hydrochloric acid or by the m. p. (83—84°) of its maleic anhydride adduct (Alder and Backendorf, *Annalen*, 1938, **535**, 101). The only other substances present in the fraction of b. p. <150° were water (1—1·5%) and furfuraldehyde (2—6%).

The liquid of b. p. 150—170° was mainly (at least 95%) furfuraldehyde, and the small residue contained some of this aldehyde and a substance insoluble in bisulphite. Distillation showed that the latter contained at least 40% of a liquid, b. p. 76—78°/14 mm., 174—176°/770 mm. (Found : C, 65·15; H, 5·5. Calc. for $C_6H_6O_2$: C, 65·4; H, 5·5%). It gave a scarlet 2 : 4-dinitrophenylhydrazone which, after recrystallisation from ethyl acetate, had m. p. 168—172° (Found : C, 50·8; H, 4·5; N, 18·4. Calc. for $C_{12}H_{10}O_5N_4$: C, 49·8; H, 3·5; N, 19·3%). 2-Acetylfuran, b. p. 173°, gives a dinitrophenylhydrazone, m. p. 222° (*A.*, 1941, ii, 112), and moreover would be expected to be soluble in aqueous bisulphite, so identification is not complete.

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19. *Reactions of Furan Compounds. Part VI. Formation of Indole, Pyrrocoline, and Carbazole during the Catalytic Conversion of Furan into Pyrrole.*

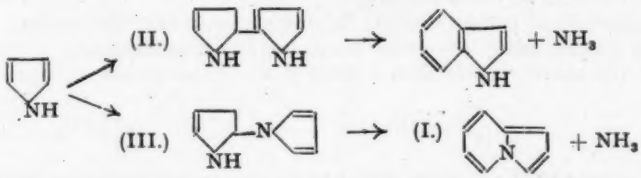
By Christopher L. Wilson.

Reaction of furan and ammonia over an alumina catalyst at 400° gave pyrrole together with smaller amounts of indole, pyrrocoline, and carbazole. The formation of these by-products is discussed.

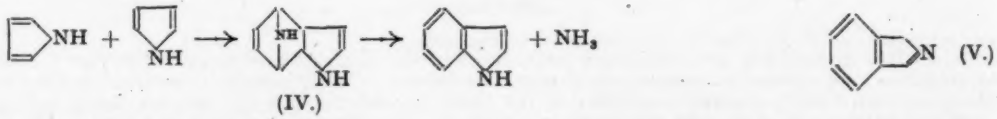
Yur'ev and Rakitin (*Ber.*, 1936, **69**, 44, 2492; D.R.P. 706,095; *Chem. Abs.*, 1942, **36**, 1957) have described the catalytic conversion of furan into pyrrole in 30% yield by passing a mixture with ammonia over an alumina catalyst at about 450°. A reinvestigation of this reaction confirmed their results and, in addition, led to the identification of three by-products, the formation of which presents an interesting problem. The compounds were indole, pyrrocoline (I) (also called indolizine), and carbazole. Pyrrocoline formed white crystals, m. p. 68—69°, with an odour like that of naphthalene, and its solution in dilute hydrochloric acid rapidly became

opalescent. No comparison with authentic pyrrocoline has been possible, but its properties identify it with considerable certainty (cf. Beilstein, Erg.-Band, XX, p. 120).

It is not immediately obvious whether the benzopyrroles arose by interaction of pyrrole with itself or with furan. The constancy of the yield of pyrrole even when conversion of furan was very low supports the first view, since, if furan had reacted with pyrrole to give a benzopyrrole, decrease in conversion should have led to a fall in the yield of pyrrole. Furthermore, pyrrole under suitable conditions, *e.g.*, under the influence of acid,



is known to be transformed into indole, and this is supposed (Allen, Gilbert, and Young, *J. Org. Chem.*, 1937, **2**, 227, 235) to proceed through a dipyrrole (II). In like manner, the formation of pyrrocoline would involve an intermediate (III) but such a compound would be expected to be rearranged on heating to an α-substituted pyrrole rather than to pyrrocoline. Alternatively, initial reaction could be supposed to lead to the formation of a normal diene adduct (IV) were it not that this type of addition in the nitrogen heterocyclic series is the exception rather than the rule.



(IV.)

It is noteworthy that no by-product possessing the *ψ-iso*indole (V) structure was isolated. *ψ-iso*Indole itself is unknown and attempts to make it have frequently given the dihydro-derivative instead, but this, too, was absent. The instability of *ψ-iso*indole has been connected (Ingold, J., 1933, 1127) with the absence of alternative positions for the unshared electrons of the nitrogen atom. In pyrrole several such possibilities exist and increased stability results from resonance between them. Reference to pyrrocoline, which has not been mentioned before in this respect, confirms this view, since many dipolar forms can be constructed. It is to be noticed that resonance between the Kekulé type of structures, which is the main contribution to the stability of the benzene ring, is absent in pyrrocoline.

It is intended to search further for *ψ-iso*indole in the reaction product, since failure to detect it may have been due to a lack of appreciation of its properties.

Experimental.

Method.—Ammonia (11 l./hr.) was bubbled through furan at 15—25°, and the mixed vapours conducted over a granular activated alumina catalyst (200 c.c., 4—6 mesh; Messrs. Peter Spence Ltd.) at 400° ± 10°. The issuing material was passed through a trap at 0° to condense water, pyrrole, and a little furan, and then through one at − 78° to catch ammonia and the rest of the furan. The catalyst deteriorated fairly rapidly and was reactivated after the passage of each g.-mol. of furan by oxidation in a stream of air at 550°.

Products.—The total amount of furan passed through the tube was 7·5 g.-mols. (510 g., 540 c.c.) of which 222 c.c. (210 g.) were recovered. Fractionation of the rest of the product gave (1) water; (2) pyrrole (95 g.), b. p. 33·5—34·5°/16 mm., 130·5—132·5°/756 mm.; (3) b. p. 84—88°/12 mm. (6·0 g., which solidified); (4) b. p. 100—130°/20 mm. (2·0 g., which partly solidified); (5) b. p. 130—135°/22 mm., 124—128°/12 mm. (10 g.); (6) residue.

Fractions (3) and (4) were treated with petrol (b. p. 60—80°), and the insoluble solid recrystallised from petrol, giving white leaflets, m. p. 68—69°, which turned black on keeping (Found: C, 81·6; H, 6·25; N, 12·5. Calc. for C_8H_7N: C, 82·0; H, 6·0; N, 11·95%). These properties and those described earlier identified the substance as pyrrocoline. Like pyrrole, it gave a red pine-splint test. Fraction (5) also gave this test (Found: C, 82·1; H, 6·55; N, 11·65%); it could not be solidified, but extraction with boiling water and cooling gave pale yellow laminæ of indole (mixed m. p.), m. p. 44—46°.

The petrol extract from fractions (3) and (4), and also fraction (5), were shaken with dilute hydrochloric acid. Basification failed to yield dihydro*iso*indole (b. p. 213°). It was considered that *iso*indole would have a b. p. about the same as, or perhaps a little higher than, indole. Fraction (5) seemed, however, to contain at least 85% of indole. The residue (6) consisted essentially of carbazole (identified by mixed m. p.), which sublimed on heating in a vacuum.

The following amounts of the three by-products were isolated: pyrrocoline, 6 g.; indole, 8 g.; carbazole, 5 g.

The author thanks Professor C. K. Ingold, D.Sc., F.R.S., for advice.

University College, London, W.C.1. [*Received, September 8th*, 1944.]

Some Aspects of the Organic Chemistry of Phosphorus and Arsenic.

THE TILDEN LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY, AT NEWCASTLE ON MARCH 17TH, 1944, AND AT LONDON ON MAY 18TH, 1944.

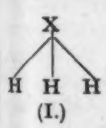
By F. G. MANN, Sc.D., D.Sc.

IT is probable that to the minds of most chemists the expression "The Organic Chemistry of Phosphorus and Arsenic" will recall most immediately the use of such compounds in chemotherapy. This applies, of course, primarily to the organic compounds of arsenic, which have two distinct applications: they are used as curative drugs for (in particular) various spirochætal infections, and also as offensive weapons in gas warfare, an application the chemical study of which may well be termed negative chemotherapy. Phosphorus differs strikingly from arsenic in that many organic compounds containing phosphorus occur naturally in animal and plant organisms, whereas apparently no organic derivatives of arsenic are of natural occurrence.* I do not, however, intend to discuss any of these subjects in this lecture. The chemotherapy of organic arsenic compounds has not of recent years undergone any striking development on the chemical side: on the physiological side, the precise mode of action of such compounds remains uncertain, and its discussion is the province of the physiologist himself. The use of organic arsenic compounds in warfare is a subject which it would be both unprofitable and undesirable to discuss at the present time. The naturally occurring organic compounds containing phosphorus are almost wholly esters of phosphoric acid, and are thus not true organic derivatives of phosphorus: to the organic chemist, therefore, the phosphorus unit in such compounds is the least interesting portion of the molecule.

I am therefore devoting this lecture to a discussion of the stereochemistry of the organic derivatives of phosphorus and arsenic, with some emphasis on the preparative methods which have been employed to obtain suitable compounds for the necessary investigations. In such a discussion the resolution of racemic compounds into their optically active forms must necessarily be prominent. There is a tendency among some chemists, more particularly those who have not kept in touch with modern chemical progress, to consider that the resolution of compounds into optically active forms is a subject which has been so exhaustively investigated in the past that it has now lost most of its theoretical significance and consequently most of its former vivid interest. It is true that no progressive organic chemist would at the present time resolve a compound with optically active forms merely to record one more optically active compound. Yet it must always be remembered that the optical activity of a compound is a physical property which throws much light on the configuration, structure, stability, and other physical and chemical properties of the compound itself. Consequently it is still actively studied, as other physical properties (for example, dipole moments, parachors, infra-red spectra, *X*-ray diffraction) are studied, for the valuable information it affords concerning the other properties of the molecule.

The organic derivatives of phosphorus and arsenic fall into two main classes, those in which these elements are in the 3-covalent condition, and those in which they are 4-covalent. Members of the first class can all be regarded as derivatives of phosphine (PH_3) and arsine (AsH_3), in which one, two, or three of the hydrogen atoms have been replaced by organic radicals: since, however, compounds having hydrogen directly linked to phosphorus or arsenic are unstable and, in particular, very readily oxidised, stereochemical work has been limited to the more stable tertiary compounds, of type PR_3 and AsR_3, where R represents an alkyl or aryl group. Members of the second class, in which the phosphorus or arsenic atom is 4-covalent, can be subdivided into three main groups. (*a*) True quaternary salts, of type $[PR_4]X$ and $[AsR_4]X$, where X is a univalent acid radical: (*b*) compounds obtained by the union of oxygen, sulphur, or selenium to the tertiary phosphine or arsine, and therefore of type $R_3P\rightarrow O$, $R_3P\rightarrow S$, $R_3P\rightarrow Se$: (*c*) compounds similarly obtained by the union of metallic salts (particularly the halides of the heavier metals) to tertiary phosphines or arsines, for example, $[R_3P\rightarrow AuCl]$. It should be noted, however, that in group (*b*), the oxygen members differ from the sulphur and selenium members in that the P—O and As—O links may have polar properties, and these compounds therefore often combine with strong acids to give salts, of type $[PR_3{\cdot}OH]Cl$ and $[AsR_3{\cdot}OH]Br$, which are akin to the true quaternary salts and thus fall systematically into group (*a*). The structure of these various types is discussed later.

In considering derivatives of 3-covalent phosphorus and arsenic, mention must be made of certain physical evidence for the configuration of these elements. Bradley (*Phil. Mag.*, 1924, **47**, 657) showed by an *X*-ray investigation that in crystalline arsenic each atom could be regarded as being situated at the apex of a tetrahedron, with its three valencies directed along the edges of the tetrahedron to join three other atoms situated at the remaining apices: from Bradley's results, the intervalency angle at the arsenic atom is 97°. It was therefore to be expected that both phosphine and arsine would have a pyramidal molecule (I, X = P or As), similar to that of ammonia. The structural constants of these molecules have been determined by Sutherland, Lee, and Wu (*Trans. Faraday Soc.*, 1939, **35**, 1373), using infra-red spectra. Their results, together with those for ammonia, are collected in Table I.



(I.)

* Although such compounds can be obtained in the laboratory by the action of living organisms; *e.g.*, trimethylarsine from arsenious oxide by the action of *Penicillium brevicaule* (Challenger *et al.*, J., 1933, 95; *Biochem J.*, 1935, **29**, 1757).

TABLE I.

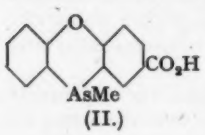
	X—H length (A.).	H—X—H angle.	Height of pyramidal molecule (A.).	Frequency of inversion per second.
NH_3	1·02	111°	0·30	2×10^{10}
PH_3	1·46	99	0·67	5×10^{6}
AsH_3	1·56	97	0·75	16×10^{4}
PD_3				6×10^{3}
AsD_3				30

Their value for the intervalency angle of arsine confirms Bradley's result for elementary arsenic, and is closely similar to that for phosphine. Their values for the frequency of inversion of the molecules per second, *i.e.*, of the oscillation of the nitrogen, phosphorus, and arsenic atom about the mean plane of the three hydrogen atoms, are of particular interest to organic chemists. The very rapid inversion of ammonia shows clearly that attempts to resolve a dissymmetric tertiary amine must fail unless this frequency can be very substantially decreased. It is much less for phosphine, and still less for arsine, but still remains very high. Replacement of the hydrogen by deuterium has a remarkable effect, however, the frequency of inversion of phosphine being reduced to *ca.* one-thousandth of its original value by this replacement, and that of arsine being reduced to the comparatively slow rate of 30 per second. If these immense reductions are caused by mere doubling of the mass of the atoms attached to the phosphorus or arsenic, the use of heavy organic radicals might, as these authors suggest, so reduce the speed of inversion that the optical resolution of (in particular) a suitable dissymmetric tertiary arsine might become practicable under suitable conditions.

Other physical evidence, for example, the electron diffraction of trimethylarsine (Springall and Brockway, *J. Amer. Chem. Soc.*, 1938, **60**, 996), although not so precise as that quoted above, confirms the value of *ca.* 97° for the arsenic intervalency angle.

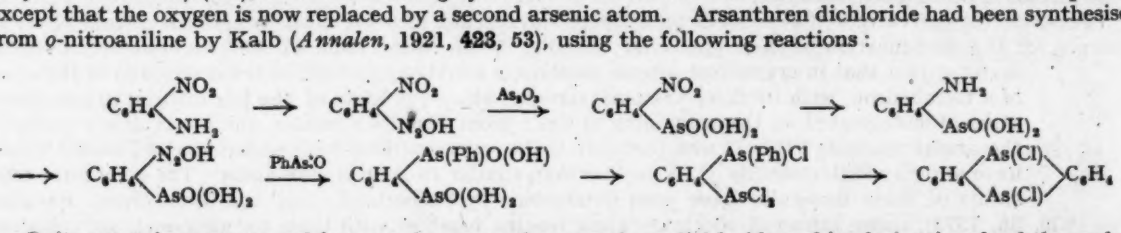
There is at present no organic evidence for the configuration of derivatives of 3-covalent phosphorus, but for similar arsenic derivatives there is evidence based both on optical and on geometric isomerism. It is significant, however, that this evidence has been obtained solely by the study of compounds in which the arsenic atom has been part of a ring system and in which the above inversion about this atom is almost certainly inhibited: all attempts to resolve a dissymmetric tertiary arsine abcAs, where a, b, and c are univalent groups, have failed (cf. Kamai, *J. Gen. Russ. Chem.*, 1940, **10**, 733), possibly owing to the nature of the groups employed.

Lesslie and Turner (J., 1934, 1170; 1935, 1051, 1268; 1936, 730) have prepared and resolved 10-methylphenoxarsine-2-carboxylic acid (II) and its 10-ethyl and 10-phenyl homologues; all three acids showed high optical stability. This optical activity might be dependent on one of two possible properties of the molecule: (*a*) the three rings might be coplanar, with the methyl group projecting above or below this plane; the three rings could be coplanar, however, only if the intervalency angle at the arsenic atom within the central ring approached 120° (Campbell, Le Fèvre, Le Fèvre, and Turner, J., 1938, 404), and this entails a most improbable increase in the normal value of this angle: (*b*) the molecule might be folded about the O . . . As axis, in order to accommodate the normal intervalency arsenic angle; in this case the three valencies of the arsenic atom might conceivably be in one plane, although this is improbable. If this folding about the O . . . As axis occurred, however, the molecule would lack a plane of symmetry, irrespective of the position of the methyl group. Lesslie and Turner consider that (*b*) is the more probable condition of the molecule. It is significant that loss of activity occurred when the compound (II) was converted into the arsine ethiodide and when the 10-phenyl homologue was converted into the arsine oxide: in both these derivatives the arsenic has become 4-covalent and tetrahedral (see later) and the expansion of the intervalency angle at the arsenic atom might allow the three rings to become coplanar. On the other hand, if the explanation (*a*) were correct, the optical activity might well have been made even more stable by the conversion of the arsenic into the 4-covalent condition.



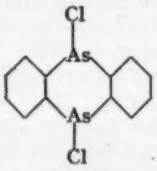
(II.)

To avoid any possible complication in the above compounds due to the cyclic oxygen atom, Chatt and Mann (J., 1940, 1184) investigated derivatives of " arsanthren dichloride " (correctly named, 5 : 10-dichloro-5 : 10-dihydroarsanthren) (III), in which the ring system is identical with that of Lesslie and Turner's compounds except that the oxygen is now replaced by a second arsenic atom. Arsanthren dichloride had been synthesised from *o*-nitroaniline by Kalb (*Annalen*, 1921, **423**, 53), using the following reactions:

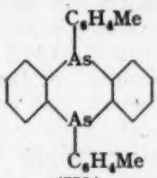


Quite apart from structural features, however, the arsanthren dichloride and its derivatives lend themselves readily to stereochemical investigation, owing to the ease and perfection with which they crystallise. If in the arsanthren molecule the intervalency arsenic atom remains *ca.* 97°, the molecule must be folded about the As . . . As axis, and the possibility of geometric isomerism immediately occurs. Chatt and Mann con-

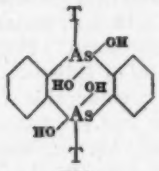
verted the 5 : 10-dichloro-compound (III) into the less reactive 5 : 10-di-*p*-tolyl compound (IV), which they subjected to fractional crystallisation. This compound, if folded about the above axis, should exist in a *cis*-



(III.)

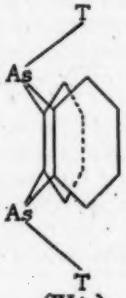


(IV.)

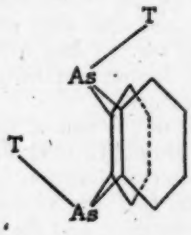


(V.)

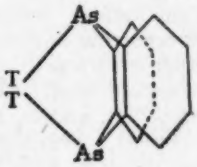
form, shown in (IVA, T = *p*-tolyl), where the arsenic atoms and tolyl groups are in the plane of the paper, whereas the more prominent benzene ring projects towards, and the other ring away from, the observer : in this *cis*-form, the two tolyl groups are both within the angle subtended by the benzene rings. The compound should also exist in a *trans*-form (IVB), in which one tolyl group is now on the opposite side of the As . . . As axis to the other. A third form, in which the two tolyl groups are again in the *cis*-position, but both on the opposite side of the axis to the benzene rings (IVc), cannot be realised, because the position of



(IVA.)



(IVB.)



(IVC.)

the two tolyl groups becomes almost coincident, a fact which can be readily demonstrated by models. Chatt and Mann succeeded in isolating the two forms, which possessed remarkable stability and underwent no interconversion even when maintained in the molten conditions for 10 minutes. When, however, bromine was added to each arsenic atom and the tetrabromide then hydrolysed to the crystalline tetrahydroxide (V), the same product was obtained from both forms : this was in accordance with theoretical expectations, because in the tetrahydroxide the intervalency ring angle of the arsenic has now become *ca.* 120° (see later) and the arsanthren ring system in consequence has become planar. Hence the basis of the former geometric isomerism has disappeared.

In discussing the stereochemistry of organic derivatives of 4-covalent phosphorus and arsenic, it is advantageous to consider the arsenic derivatives first, because they have been more widely investigated and have yielded richer results than those of phosphorus. This position has arisen because the organic arsenic compounds have proved much more attractive to the practical chemist than the phosphorus compounds. The arsenic derivatives often crystallise readily and with great beauty, whereas the phosphorus analogues often show strong disinclination to crystallise. Furthermore, the Bart reaction for the synthesis of arylarsonic acids, and the ready reduction of many arsonic acids and tertiary arsine oxides to the corresponding arsenious compounds—reactions of the greatest synthetic value—have no counterpart in the chemistry of phosphorus derivatives, the preparation of which in consequence frequently proves of much greater difficulty.

Summarising briefly the stereochemistry of 4-covalent nitrogen derivatives for comparison, it will be recalled that the first resolution of a quaternary salt containing an asymmetric nitrogen atom, phenylbenzylmethylallylammonium iodide, was accomplished in 1899 by Pope and Peachey (J., 1899, **75**, 1127), and that of a tertiary amine oxide, phenylmethylethylamine oxide, in 1908 by Meisenheimer (*Ber.*, 1908, **41**, 3966) : finally, chemical evidence for the tetrahedral configuration of the nitrogen atom in quaternary salts was obtained in 1925 by Mills and Warren (J., 1925, **127**, 2507) by the optical resolution of 4-phenyl-4'-carbethoxybispiperidinium-1 : 1'-spiran bromide. Pope and Peachey's work stimulated many chemists to attempt in particular the preparation and optical resolution of a similar quaternary arsonium salt, of type [abcdAs]X, since it was exceedingly unlikely that either phosphorus or arsenic compounds would possess a configuration essentially different from that of the corresponding types of nitrogen compounds. All attempts to isolate optically stable arsonium salts failed, however, although Burrows and Turner (J., 1921, **119**, 426) obtained phenyl-α-naphthylbenzylmethylarsonium iodide having a maximum experimental rotation α_D 0·1°, $[M]_D$ 12°, in alcoholic acetone, but the activity of the solution rapidly disappeared at room temperature. Similarly Kamai (*Ber.*, 1933, **66**, 1779; *J. Gen. Chem. Russia*, 1934, **4**, 184) obtained *p*-tolylbenzylethyl-*n*-propylarsonium iodide with an experimental rotation of α_D + 0·22°, and $[M]_D$ + 45°, but this salt also rapidly lost this small rotation when in acetone solution at room temperature. The difference between the difficulty

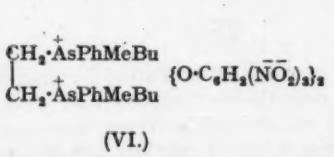
attending the resolution of such arsonium salts and the ease with which many similar ammonium salts had been resolved was striking, and at first difficult to explain. It was known, however, that several optically active quaternary ammonium nitrates and sulphates showed considerably stability in solution, whereas the corresponding halides, although usually optically stable in aqueous solution, often showed rapid racemisation in solvents such as chloroform. Pope and Harvey (J., 1901, **79**, 831) suggested that this racemisation was due to the formation of a "dissociation-equilibrium," of the type [abcdN]I $\rightleftarrows$ abcN + dI, in solution, a suggestion for which considerable physical evidence was later forthcoming. This explained the optical stability of the nitrates and sulphates, which clearly could not undergo this facile dissociation.

Burrows and Turner (*loc. cit.*) suggested that the failure to obtain optically stable arsonium salts was due to the formation of a similar " dissociation-equilibrium " in solution. It is noteworthy that for synthetic reasons all arsonium salts whose resolution had been attempted had contained at least one alkyl group attached to the arsenic atom, an obviously necessary condition for the establishment of the dissociation-equilibrium. Burrows and Turner obtained some evidence for the formation of this equilibrium, for they showed that phenyldimethylarsine, when treated at room temperature with an excess of ethyl iodide, furnished the expected phenyldimethylethylarsonium iodide, but also afforded phenyltrimethylarsonium iodide. The formation of

$$PhMe_2As + EtI \rightleftarrows [PhMe_2EtAs]I \rightleftarrows PhMeEtAs + MeI \qquad PhMe_2As + MeI \rightleftarrows [PhMe_3As]I$$

the latter salt can be reasonably explained only on the assumption that the former salt established an equilibrium both with the two original components and also with phenylmethylethylarsine and methyl iodide. The methyl iodide thus generated, however, then reacted also with the phenyldimethylarsine, furnishing the phenyltrimethylarsonium iodide. Burrows and Turner obtained several other examples of similar interchange of alkyl groups occurring at room temperature.

More recently, further evidence to confirm, if not to prove, the existence of these dissociation equilibria of arsonium salts has been obtained. Chatt and Mann (J., 1939, 610) prepared ethylene-αβ-bis(phenylmethyl-*n*-butylarsonium picrate) (VI), and by fractional crystallisation separated it into two isomeric forms, m. p. 113—115° and 139·5—140·5°. This salt contains two similar asymmetric arsonium atoms, and one of the two forms isolated must therefore have been the racemic and the other the *meso*-form, the type of isomerism being identical with that shown by the tartaric acids. The two forms of the picrate were highly stable and



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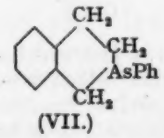

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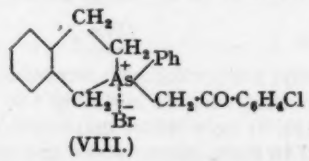


(VIII.)

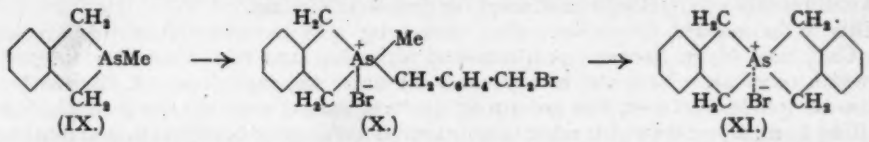
underwent no interconversion even in boiling alcohol. Such an interconversion, had it occurred, would have involved a change of configuration of one of the arsonium atoms. If such a change of configuration is dependent on the formation of a dissociation-equilibrium, the stability of the two forms is at once explained, because such a dissociation would have entailed the formation of the tertiary arsine and an alkyl picryl ether, which is obviously exceedingly unlikely to occur.

Chemical evidence for the validity of the dissociation-equilibrium theory of optical instability of arsonium salts could be obtained by the resolution into optically stable forms of an arsonium salt which for structural reasons could not so dissociate in solution. The structural stability might be peculiar to the particular compound studied, or (a more general case) it could be obtained by preparing a dissymmetric arsonium salt [abcdAs]X, in which four unlike *aryl* groups were linked to the arsenic atom, so that dissociation almost certainly could not occur.

The former case has been realised by Holliman and Mann (J., 1943, 551), who showed that *o*-β-bromoethylbenzyl bromide, $C_6H_4(CH_2Br)(CH_2{\cdot}CH_2Br)$, reacted with phenyldichloroarsine in the presence of sodium to give 2-phenyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline (VII), a compound in which the heterocyclic ring had very considerable stability and could only with difficulty be ruptured. This compound was combined with *p*-chlorophenacyl bromide to give 2-phenyl-2-*p*-chlorophenacyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinolinium bromide (VIII). This particular arsonium salt was chosen because there was evidence that the *p*-chloro-group stabilised the phenacyl radical, and greatly strengthened its union to the arsenic atom. This salt was resolved through the corresponding bromocamphorsulphonates, and the *d*- and the *l*-arsonium picrate were isolated having $[M]_D$ + 457° and − 450° respectively: the *l*-iodide had moreover $[M]_D$ − 354° and remained optically unchanged in chloroform solution at room temperature over a period of five days. This optical activity, both in its order and in its stability, is in marked contrast to previous results, and is undoubtedly due, I consider, to the chemical stability of the iodide preventing the formation of a dissociation-equilibrium.

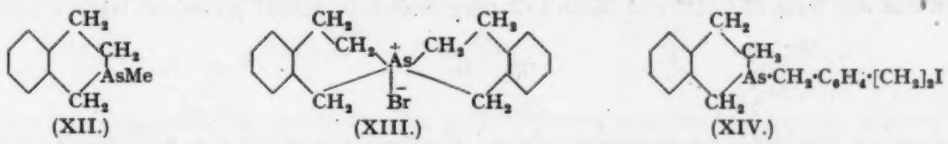
Striking evidence for the chemical stability of the heterocyclic ring in the 1 : 2 : 3 : 4-tetrahydro*iso*arsinolines (such as VII) has recently been obtained in the Cambridge laboratories. Lyon and Mann (this vol., p. 30) had shown that *o*-xylylene dibromide reacts with methyldichloroarsine in the presence of sodium to form 2-methyl*iso*arsindoline (IX). This tertiary arsine united readily with a further molecule of *o*-xylylene dibromide to form the arsonium salt, 2-*o*-(bromomethyl)benzyl-2-methyl*iso*arsindolinium bromide (X), which when heated lost methyl bromide, forming *As-spiro*-bis*iso*arsindolinium bromide (XI), a highly crystalline

water-soluble salt. This constitutes the first synthesis of an *As-spiro*cyclic salt having all the four arsenic valencies joined directly to carbon atoms. A precisely similar synthesis was therefore carried out by Holliman



(IX.) (X.) (XI.)

and Mann, who united 2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline (XII) with *o*-β-bromoethylbenzyl bromide to give the arsonium salt (similar in type to X), which on heating also lost methyl bromide, furnishing *As-spiro*-bis-1 : 2 : 3 : 4-tetrahydro*iso*arsinolinium bromide (XIII). In this salt the arsenic atom is symmetric



(XII.) (XIII.) (XIV.)

(unlike that in VIII), but the tetrahedral disposition of the ring systems around the central arsenic atom causes the compound to possess molecular dissymmetry. This salt was also resolved through its bromocamphorsulphonates, and the *d*- and the *l*-arsonium iodide isolated, having $[M]_D$ + 342° and − 344° respectively in chloroform solution. These solutions underwent no change in rotation at room temperature during a period of one month, and the salts therefore possessed very high optical stability. Had any rupture of one of the heterocyclic rings occurred in solution, to give, for example, even a small proportion of the tertiary arsine (XIV) in equilibrium with the parent compound, racemisation must certainly have occurred, probably speedily.

For the synthesis of a dissymmetric tetra-arylarsonium salt, [abcdAs]X, the necessary triarylarsine, abcAs, can be readily prepared, the critical stage being the addition of a fourth aryl group to the arsenic atom to furnish the required arsonium ion, since simple addition of an aryl halide to the arsine is clearly impossible. For this purpose, however, two distinct reactions are available. Blicke and Monroe (*J. Amer. Chem. Soc.*, 1935, **57**, 720) have shown that triphenylarsine oxide, when treated with phenylmagnesium bromide and then with hydrobromic acid, yields tetraphenylarsonium bromide, [Ph_4As]Br : this reaction appears, however, to have limited application for the synthesis of tetra-aryl arsonium salts (Blicke and Cataline, *ibid.*, 1938, **60**, 423). Alternatively, Chatt and Mann (J., 1940, 1192) have shown that triphenylarsine, when heated with aluminium chloride and bromobenzene, also furnishes tetraphenylarsonium bromide. This reaction is of wide application, since the use of triaryl phosphines and stibines, in place of the arsine, similarly yields the corresponding tetra-aryl-phosphonium and -stibonium salts respectively. The mechanism of this reaction has been elucidated by Lyon and Mann (J., 1942, 666), who showed that triphenylarsine unites readily with aluminium chloride to give the very reactive trichlorotriphenylarsinealuminium, [$Ph_3As\rightarrow AlCl_3$]. The reactivity of the latter is shown by the fact that it undergoes ready atmospheric oxidation at room temperature, forming triphenylarsine oxide, a reaction which is not shown by pure triphenylarsine under these conditions. It also readily reacts with hot bromobenzene to give the salt, $[\overset{+}{Ph_4As}][\overset{-}{AlCl_3Br}]$, which of course on subsequent treatment with hydrobromic acid furnishes tetraphenylarsonium bromide. This aluminium chloride reaction has recently been utilised by Mann and Watson to prepare a tetra-arylarsonium salt of the required type, the aryl groups being inserted in the following order :

$$PhAs{:}O \xrightarrow{p\text{-}C_6H_4Me\cdot N_2OH} Ph(p\text{-}C_6H_4\cdot Me)AsO(OH) \xrightarrow{SO_2+HCl} Ph(p\text{-}C_6H_4Me)AsCl \xrightarrow{p\text{-}C_6H_4Cl\cdot MgI}$$

$$Ph(p\text{-}C_6H_4Me)(p\text{-}C_6H_4Cl)As \xrightarrow[+\,AlCl_3]{m\text{-}C_6H_4MeBr} [Ph(p\text{-}C_6H_4Me)(m\text{-}C_6H_4Me)(p\text{-}C_6H_4Cl)As]Br$$

This salt furnished in turn the crystalline and less soluble arsonium iodide. Clearly the latter cannot dissociate in solution, and if our attempts to resolve it into optically stable forms prove successful, very strong evidence for the dissociation-equilibrium theory of optical instability will have been obtained.

Turning now to those compounds formed by the union of a tertiary arsine with a Group VI element, it is noteworthy that no success has attended various attempts to resolve a dissymmetric tertiary arsine oxide, of type abcAs→O, although by analogy with Meisenheimer's tertiary amine oxides, such a resolution should be practicable under suitable conditions. The structure of such arsine oxides and their derivatives presents some very interesting points, however, and will be discussed later with the analogous tertiary phosphine oxides.

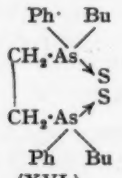
A sulphide of similar type, *p*-carboxyphenylmethylethylarsine sulphide (XV), was prepared by Mills and Raper (J., 1925, **127**, 2479), using the following reactions :

$$p\text{-}CH_3\cdot C_6H_4\cdot As{:}O \xrightarrow[+\,SO_2]{MeI+NaOH} p\text{-}CH_3\cdot C_6H_4(Me)AsI \xrightarrow{EtMgI} p\text{-}CH_3\cdot C_6H_4(Me)(Et)As \xrightarrow{O}$$

$$p\text{-}CO_2H\cdot C_6H_4(Me)(Et)As\rightarrow O \xrightarrow{H_2S} p\text{-}CO_2H\cdot C_6H_4(Me)(Et)As\rightarrow S \quad (XV.)$$

The acid was resolved through its brucine and morphine salts, and obtained in *d*- and *l*-forms, having $[M]_{5780}$ + 51° and − 52° respectively in alcoholic solution. This acid had considerable optical stability: an aqueous solution of its sodium salt was optically unaffected by prolonged boiling.

This stability is in marked contrast to that shown by ethylene-αβ-bis(phenyl-*n*-butylarsine sulphide) (XVI), which Chatt and Mann (*loc. cit.*) prepared and separated into two isomerides, m. p. 113—116° and 121°, one of which must have been the racemic and the other the *meso*-form (cf. the metho-picrates, VI). In this diarsine-disulphide, however, the lower-melting form passed very readily (even in hot alcohol) into the higher-melting form, a process which must have involved a change of configuration of one of the 4-covalent arsenic atoms. It is difficult to suggest a probable mechanism for the racemisation of an arsine sulphide, other than by the formation once again of a dissociation-equilibrium, now of the type abcAs→S ⇄ abcAs + S. The question at once arises as to the reason why Mills and Warren's compound should possess great optical stability, whilst one form of Chatt and Mann's diarsine-disulphide should possess so labile a configuration.



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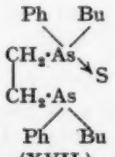
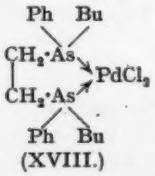


(XVII.)



(XVIII.)

I think the probable explanation is that in the preparation of the diarsine-disulphide (XVI) by the direct addition of sulphur to the di-tertiary arsine, the first atom of sulphur unites readily and probably very firmly to the arsenic, to give the diarsine-monosulphide (XVII). The 4-covalent (upper) arsenic atom now acquires a positive charge, which, although much weaker than that on a true arsonium ion, is strong enough to exert an inductive effect through the methylene groups, and so to weaken the normal reactivity of the lone pair of electrons on the second (lower) arsenic atom. This reduced reactivity does not prevent this arsenic atom combining with the second sulphur atom to give the diarsine-disulphide (XVI), but does weaken its attachment, so that in solution the equilibrium, diarsine-disulphide ⇄ diarsine-monosulphide + sulphur, occurs. This dissociation could not actually be detected by molecular weight determinations, but clearly the degree of dissociation need be only very small to cause a rapid change in configuration: in these circumstances the complete conversion of the less stable into the more stable form is to be expected.

It is noteworthy that the palladochloride derivative (XVIII) of the diarsine (Chatt and Mann, J., 1939, 1622) was separated into two similar forms, m. p. 172—174° and 185—186°, which possessed great configurational stability, and each form could be maintained even in the molten condition without detectable conversion into the other. In this compound, however, the ring system is undoubtedly very stable, and is not ruptured by mere dissolution or fusion: consequently there is no mechanism by which change of configuration of the arsenic atoms can occur.

It may be added that arsenic can show a covalency of six and therefore apparently an octahedral configuration, for Rosenheim and Plato (*Ber.*, 1925, **58**, 2000) have obtained tripyrocatechylarsenic acid, $H[(C_6H_4O_2)_3As]$, in optically active forms. In this and similar compounds, however, the arsenic is linked to oxygen and not directly to carbon, and their consideration is therefore outside the scope of this lecture.

Turning to the organic derivatives of 4-covalent phosphorus, it is a striking fact that in spite of many attempts to resolve a dissymetric phosphonium salt, of type [abcdP]X, no success has hitherto been achieved (cf. Michaelis, *Annalen*, 1901, **315**, 54; Pope and Gibson, J., 1912, **101**, 753; Wedekind, *Ber.*, 1912, **45**, 2933; Radcliffe and Brindley, *Chem. and Ind.*, 1923, **42**, 64; Meisenheimer *et al.*, *Annalen*, 1926, **449**, 224; Kamai, *J. Gen. Chem. Russ.*, 1932, **2**, 526). Although greater experimental difficulties have made this work more restricted, both in range and in application, than that on similar arsonium salts, I am convinced that the failure to resolve the phosphonium compounds has been caused by the same factor that underlies the arsonium compounds, namely, the formation of dissociation-equilibrium, [abcdP]X ⇄ abcP + dX, in solution, although Wedekind (*loc. cit.*) has adduced some evidence to disprove the existence of such dissociation. It is, however, significant that all the phosphonium salts investigated by the above workers have possessed at least one alkyl group attached to the phosphorus atom, and dissociation should thereby have been favoured. The problem can be satisfactorily solved only by the means described above for similar arsonium salts, namely, by the synthesis and resolution of a dissymmetric phosphonium salt which, by virtue of its structure, cannot dissociate in solution.

Considerable interest attaches to the structure and properties of the tertiary phosphine oxides, of general formula $R_3P\rightarrow O$, where R may be an alkyl or aryl group, and to their arsenic analogues: the aryl derivatives have been most intensively studied, since the triarylphosphines (unlike the alkyl analogues) are crystalline solids at room temperature, and their oxides are also stable crystalline compounds, usually devoid of the deliquescent properties of trialkylphosphine oxides. Whereas, however, the tertiary amine oxides, $R_3N\rightarrow O$, contain a true co-ordinate link, *i.e.*, the link consists of two electrons both contributed by the nitrogen atom, in the phosphine oxides the P→O distance is intermediate between that required for a single and that for a double link: this link is probably therefore a resonance hybrid between a true co-ordinate link and a double bond.

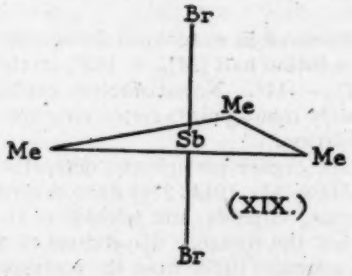
[Chemists have no symbol for such a bond, and hence I am retaining a conventional → sign in these compounds.] This resonance link may retain sufficient polarity, however, for the tertiary phosphine oxides to unite with strong acids, *e.g.*, hydrobromic acid, forming salts such as $[R_3P{\cdot}OH]Br$, a class of compounds whose arsenic analogues, $[R_3As{\cdot}OH]Br$, are even more frequently encountered. The properties of these " hydroxybromides " show clearly that they are true salts, the bromine being present as ions, and the hydroxy-group being therefore covalently linked to the phosphorus (or arsenic). If, however, a tertiary phosphine is treated with one molecular equivalent of bromine, the tertiary phosphine bromide, R_3PBr_2, is formed : such compounds are reasonably stable in the absence of water, and can often be recrystallised unchanged. The stability of the bromine atoms is greatly affected by the nature of the organic groups R (Mann and Chaplin, J., 1937, 527), but usually boiling water causes hydrolysis of one bromine atom to give the hydroxybromide, $R_3P(OH)Br$, whilst hot caustic alkaline solution causes complete hydrolysis to the dihydroxide, $R_3P(OH)_2$. The stability

$$R_3PBr_2 \longrightarrow [R_3P{\cdot}OH]Br \longrightarrow R_3P(OH)_2 \longrightarrow \begin{matrix} R_3P{\cdot}OH \\ \diagup \\ O \\ \diagdown \\ R_3P{\cdot}OH \end{matrix} \longrightarrow R_3P{\rightarrow}O$$

of the tertiary phosphine and arsine dihydroxides varies between wide limits, however, because it also is determined by the nature of the attached groups R. Some dihydroxides are exceedingly stable; others undergo dehydration to a definite crystalline intermediate " sesqui " stage, $(R_3P{\cdot}OH)_2O$; others may undergo such ready dehydration to the oxide, $R_3P{\rightarrow}O$, that the existence of the dihydroxide is difficult to prove. In view of this wide diversity of properties, it is unlikely that any one structure can be rigidly applied to all tertiary phosphine and arsine dihydroxides. Three possible structures can be briefly discussed :

(a) *The ionic structure.* In view of the above preparation of the dihydroxides from the ionic hydroxybromides, it is reasonable to assume that the former may also have an ionic structure $[R_3P{\cdot}OH]OH$. There is little doubt from Meisenheimer's work (discussed below) that in favourable circumstances this hydroxy-cation, $[R_3\overset{+}{P}{\cdot}OH]$, can exist in aqueous solution.

(b) *The resonance structure.* The properties of the tertiary phosphine (and arsine) dibromides show that they are true covalent compounds, and almost certainly are not salts of type $[R_3PBr]Br$. It is noteworthy, moreover, that in the analogous trimethylstibine dihalides, Me_3SbX_2 (where X represents Cl, Br, or I), Wells (*Z. Krist.*, 1938, **99**, 367) has shown by *X*-ray analysis that the antimony atom lies in the centre of an equilateral triangle, whose apices are occupied by the methyl groups (XIX) : the halogen atoms (for example, the bromine atoms) lie on an axis running through the antimony atom at right angles to the triangle. The important point is, however, that the two Sb—Br distances are identical and are intermediate between that required for a covalent and that for an electrovalent bond, *i.e.*, the bond is a resonance linkage. It is highly probable, therefore, that the analogous tertiary phosphine (and arsine) dihalides have a similar construction and configuration. Consequently it is possible that in certain cases the corresponding dihydroxides also have this constitution (XX), the hydroxy-groups being joined to the phosphorus or arsenic by identical resonance



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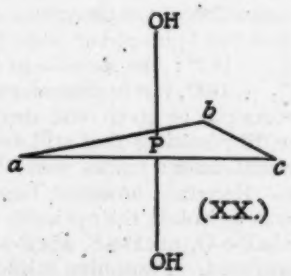


(XX.)

links. The adoption of this structure may therefore be the explanation of the high stability shown by certain phosphine and (in particular) arsine dihydroxides. An *X*-ray investigation of such compounds would be of the greatest interest. This structure gives the C—As—C angle a value of 120°, unless it is distorted by the three organic radicals being of widely different shape or mass. This value accords well with the fact that the two isomeric forms of 5 : 10-di-*p*-tolyl-5 : 10-dihydroarsanthren give the same tetrahydroxide, in which the three fused rings are undoubtedly coplanar (p. 67).

(c) *The hydrogen bond structure.* It has been suggested (Sidgwick, " The Organic Chemistry of Nitrogen," 2nd Edition, 1937, 168) that the feeble basic properties of the tertiary amine dihydroxides, $R_3N(OH)_2$, compared with those of quaternary ammonium hydroxides, indicate that the amine dihydroxides have the structure $R_3N{-}O{\cdot}{\cdot}{\cdot}HOH$, and therefore consist of the amine oxide linked through a hydrogen bond to a water molecule. The presence of the above resonance links in the amine dihydroxides would, however, account satisfactorily for the low basicity. It is unlikely, however, that a similar structure, $R_3P{-}O{\cdot}{\cdot}{\cdot}HOH$, could apply to the tertiary phosphine dihydroxides, because this would imply that the above " sesqui " compounds $(R_3P{\cdot}OH)_2O$, had the structure $R_3P{-}O{\cdot}{\cdot}{\cdot}HOH{\cdot}{\cdot}{\cdot}O{-}PR_3$. But in the arsenic series, the two intermediate stages, the hydroxy-

oxybromide (XXI) and the oxydibromide (XXII), are encountered as definite crystalline compounds (Lyon and Mann, J., 1942, 666). These cannot be formulated as derivatives of the above hydrogen-bond compound,

(XXI.) $\begin{matrix} R_3As{\cdot}OH \\ > O \\ R_3AsBr \end{matrix}$ $\qquad$ $\begin{matrix} R_3AsBr \\ > O \\ R_3AsBr \end{matrix}$ (XXII.)

but can be readily formulated as derivatives of anhydrides obtained from either the above ionic or the resonance dihydroxides.

These considerations have a direct bearing on Meisenheimer's work (*Ber.*, 1911, **44**, 356; *Annalen*, 1926, **449**, 224) on the preparation and resolution of tertiary phosphine oxides, an investigation which, owing largely to retarded crystallisation, took about eleven years to complete. Meisenheimer prepared phenylmethylethylphosphine, and converted it into the oxide (XXIII): the latter had the normal polar properties and combined with *d*-bromocamphorsulphonic acid to give the salt (XXIV), which, after repeated crystallisation from ethyl acetate, yielded the optically pure *d*-phenylmethylethylhydroxyphosphonium *d*-bromocamphorsulphonate. The latter in aqueous solution had $[M]_D$ + 313°,* which fell to $[M]_D$ +306° on the addition of one equivalent of sodium hydroxide: no indication of even partial racemisation is recorded for either solution. Meisenheimer argued that, since ammonium *d*-bromocamphorsulphonate at equivalent concentration in water has $[M]_D$ + 267°, the phosphorus cation in (XXIV) has $[M]_D$ + 39°. Meisenheimer then passed dry ammonia

PhMeEtP→O (XXIII.) $\qquad$ [PhMeEtP·OH]*d*-$C_{10}H_{14}OBrSO_3$ (XXIV.) $\qquad$ Ph(CH_2Ph)MeP→O (XXV.)

through a benzene solution of the above bromocamphorsulphonate (XXIV), whereby the bromocamphorsulphonic acid was split off directly as the insoluble ammonium salt. The filtered solution on evaporation gave the *d*-phosphine oxide (XXIII), which had high optical stability and distilled under reduced pressure without detectable racemisation. This is what we should now expect, as there is no mechanism by which the phosphine oxide, if chemically stable, could racemise during this process. The crystalline deliquescent oxide so obtained had $[M]_D$ + 38° in aqueous solution, $[M]_D$ + 40° in water containing one equivalent of hydrochloric acid, and $[M]_D$ + 47° in benzene solution. Meisenheimer asserted that the second of these values represents the rotation of the salt [PhMeEtP·OH]Cl, and compares this rotation with that predicted above for this cation. These results leave little doubt, I think, that the oxide in aqueous solution also forms this cation, and that an optically active ionic hydroxide, [PhMeEtP·OH]OH, exists in the aqueous solution. Convincing evidence for this, however, would be afforded by the conversion of Meisenheimer's phosphine oxide (XXIII) by hydration into a definite crystalline dihydroxide without loss of optical activity.

Rather different factors apply, however, to phenylbenzylmethylphosphine oxide (XXV), which Meisenheimer combined with *d*-camphorsulphonic acid, and then by recrystallisation isolated both *l*-phenylbenzylmethylhydroxyphosphonium *d*-camphorsulphonate and its diastereoisomeride. The former salt, when treated even in hot aqueous solution with an excess of ammonia, deposited the crystalline *l*-phosphine oxide (XXV), which clearly therefore possessed such feebly polar properties that it does not form a dihydroxide. In this case, therefore, the action of alkalis on the hydroxy-salts is apparently the direct fission of the corresponding acid and immediate formation of the phosphine oxide.

It is noteworthy that the *l*-phosphine oxide (XXV), dissolved in water containing one equivalent of hydrochloric acid, had $[M]_D$ − 167°: the *d*-oxide in aqueous solution had $[M]_D$ + 162°, in the above hydrochloric acid solution had $[M]_D$ + 168°, but in chloroform had $[M]_D$ − 17°. No satisfactory explanation of this change of rotation in chloroform can be given, and there are clearly many points concerning the structure of tertiary phosphines and arsine dihydroxides that still await elucidation.

Until recently Meisenheimer's oxides were the only true organo-phosphorus derivatives to be obtained in optically active form. Recently, however, Davies and Mann (J., 1944, 276) have described an investigation the object of which was to isolate the optically active oxide, sulphide, and selenide of the same dissymmetric tertiary phosphine, abcP→O, abcP→S, abcP→Se, so that the rotatory dispersions of the three compounds could be critically compared. Phosphine sulphides and selenides differ from the corresponding oxides in that the P—S and P—Se link is almost non-polar, and cannot be used for salt formation. Consequently compounds which carried an acidic or basic group for subsequent salt formation had to be prepared. Davies and Mann's results are concerned primarily with the synthetic methods developed for this purpose, and their application to the preparation of several apparently suitable racemic phosphine sulphides. Only one of the latter was resolved, however, and its synthesis is outlined below, because it illustrates the greater difficulty and complexity attending the preparation of such phosphorus compounds compared with those of similar arsenic compounds, such as (XV).

$$C_6H_5{\cdot}OMe \xrightarrow{PCl_3+AlCl_3} (p\text{-}C_6H_4{\cdot}OMe)Cl_2P \xrightarrow{HgPh_2} Ph(C_6H_4{\cdot}OMe)ClP \xrightarrow{n\text{-}BuMgBr}$$

$$Ph(C_6H_4{\cdot}OMe)BuP \xrightarrow{HI} Ph(C_6H_4{\cdot}OH)BuP \xrightarrow[+NaOH]{Ph{\cdot}COCl} Ph(C_6H_4{\cdot}O{\cdot}COPh)BuP \xrightarrow{S}$$

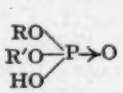
$$Ph(C_6H_4{\cdot}O{\cdot}COPh)BuP{\rightarrow}S \xrightarrow{Hydrolysis} Ph(C_6H_4{\cdot}OH)BuP{\rightarrow}S \xrightarrow[+NaOH]{CH_2Br{\cdot}CO_2Et} Ph(C_6H_4{\cdot}O{\cdot}CH_2{\cdot}CO_2H)BuP{\rightarrow}S$$

(XXVI.)

* These rotations are the amended values given in Meisenheimer's second paper.

The final product, phenyl-*p*-(carboxymethoxy)phenyl-*n*-butylphosphine sulphide (XXVI), was resolved by combination with α-phenylethylamine, and the free acid ultimately isolated in *d*- and *l*-forms, having $[M]_D$ + 9·6° and − 9·7° respectively in benzene solution. Neither this acid in benzene, nor its ammonium salt in water, showed any tendency to racemise.

In earlier years, synthetic difficulties in the preparation of organo-phosphorus compounds had induced chemists to investigate the possibility of resolving esters (XXVII) and amides (XXVIII) of phosphoric acid (Caven, J., 1902, **81**, 1362; Luff and Kipping, J., 1909, **95**, 1993) and also phosphonic acids (XXIX) (Pope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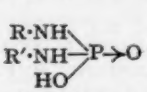
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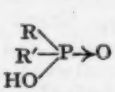
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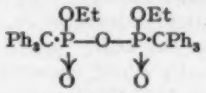

(XXX.)

and Gibson, J., 1912, **101**, 740). It is now realised that such attempts must have been fore-doomed to failure, because ionisation of these acids in aqueous solution would have been immediately followed by resonance in the phosphorus anion, which thus would have become symmetric. It is noteworthy, however, that Hatt (J., 1933, 776) has separated ethyl triphenylmethylpyrophosphonate (XXX) into two forms, m. p. 222—223° and 228—231°; since the compound contained two similar asymmetric phosphorus atoms, one of these forms must have been the racemic, and the other the *meso*-form. In accordance with expectation, however, both forms on hydrolysis gave the same acid, in which resonance of the anion must necessarily make both phosphorus atoms symmetric.

It must be emphasised that the optical resolution of the various 4-covalent phosphorus and arsenic compounds described above does not prove that these atoms have the tetrahedral configuration—it shows solely that the phosphorus or arsenic atom cannot be in the same plane as the other four groups to which it is attached. Although there is thus no direct chemical evidence that the 4-covalent arsenic and phosphorus atoms have the tetrahedral configuration, the study of other types of organic derivatives of these elements has provided unambiguous evidence on this point. Mann, Purdie, and Wells (J., 1936, 1503; 1937, 1828) have shown that, whereas tertiary phosphines and arsines combine with aurous salts to give simple non-ionic compounds of type $[R_3P\rightarrow AuCl]$, they combine with cuprous iodide and argentous iodide to form more complex non-ionic derivatives of type $[R_3As\rightarrow CuI]_4$ and $[R_3P\rightarrow AgI]_4$. The complete structure of one member, tetrakis(monoiodotriethylarsine copper), $[Et_3As\rightarrow CuI]_4$, has been established, and the configuration of the 4-covalent arsenic, 4-covalent cuprous, and 3-covalent iodine atoms thus determined. The arsenic atoms in this compound lie each at the centre of a tetrahedron, having one cuprous and three carbon atoms at its apices: the isomorphism of the corresponding phosphine compounds shows that the 4-covalent phosphorus atom also has the tetrahedral configuration.

Further evidence has been obtained by the crystallographic examination of the "bridged" compound which trimethylarsine forms with palladous bromide, namely, dibromobis(trimethylarsine)-μ-dibromodipalladium, $[(Me_3As)BrPdBr_2PdBr(Me_3As)]$: the complete structure of this compound has been elucidated by *X*-ray analysis (Mann and Wells, J., 1938, 702; Wells, *Proc. Roy. Soc.*, 1938, *A*, **167**, 169), and here again the 4-covalent arsenic atoms have the tetrahedral configuration.

OBITUARY NOTICES.

JOHN KEITH ROBERTS.

1897—1944.

JOHN KEITH ROBERTS, only son of H. C. Roberts of Melbourne, Australia, entered Melbourne University with a particular interest in Chemistry. Mainly owing to the inspiration of Professor T. S. Laby he was attracted to the study of Physics. Roberts had a distinguished academic record at Melbourne, becoming Professor Laby's first research student and eventually Demonstrator in Physics. He came to England with the aid of an 1851 Studentship to work under Lord Rutherford at the Cavendish Laboratory and as a member of Trinity College. Here he was engaged on the determination of the mechanical equivalent of heat, gaining the Ph.D. degree in 1923.

In 1922 he joined the scientific staff of the National Physical Laboratory and became a member of the Heat Department, being promoted to Scientific Officer a year later. His work on the thermal conductivity and thermal expansion of crystals of metallic bismuth which was published in the *Proceedings* of the Royal Society led him to investigate the mechanism of heat transfer across liquid metal interfaces. During this investigation in 1924 he developed what was at first thought to be simple arthritis in his hip, but this turned out to be tubercular trouble. He was sent to a clinic in Switzerland, where he had to remain nearly four years. During this period, spent mainly in bed, he took the opportunity of writing his text book on "Heat and Thermodynamics" (now in its third edition), which is one of the standard works on the subject.

He returned to England in 1928 as a Mosely Research Student of the Royal Society and continued to work on problems connected with heat. He became interested in the operation of the Pirani gauge and published during the five years as a Mosely Student, three papers on the exchange of energy between gas atoms and solid surfaces.

In 1933 Roberts was appointed Assistant Director of Research in the Colloid Science Laboratory, Cambridge. He was engaged for nearly six years, until the outbreak of war, in exploring the conditions of formation and the stability of monolayers of gases found on metallic wires. He developed two powerful methods of attack. In the first he showed how the change in accommodation coefficient of the rare gases could be used to examine the formation of monolayers of adsorbable gases. The other consisted in utilising the wire, necessarily a thin one, on which gas adsorption took place as one arm of a Wheatstone Bridge, the heat of adsorption causing a measurable change in the resistance of the wire. A number of papers testify to the great skill displayed in the experimental work and the thoroughness with which the theoretical avenues were explored.

At the outbreak of war Roberts went as Senior Scientific Officer to a Naval Research Establishment on the Clyde and subsequently to one on the Forth, where he was in charge of all the scientific work. Here he was eminently successful and proved himself to have a flair for organisation. In 1942 he was appointed to the very important post of Chief Scientist at the Anti-Submarine Establishment at Fairlie. At this critical moment in the Battle of the Atlantic this was a position of the highest responsibility. New and better detecting equipment was urgently needed, and the Establishment had to be completely reorganised, and new methods introduced in the shortest possible time. By his firm and original handling of this enormous task Roberts achieved one of the most striking successes of the war.

In the autumn of 1943 Roberts was chosen to lead a small party of naval scientists to the United States. He thoroughly enjoyed this and felt quite correctly that the visit had been a great success.

After his return from America in November, 1943, he felt he had still much to do in the Navy, but he was looking forward eagerly to his return to Cambridge, where he had been elected a Fellow of Christ's College, and hoped to direct the Mond Cryogenic Laboratory, a post for which he was eminently suited.

In 1924 he had married the elder daughter of H. W. Sanderson. He was supremely happy in his home, and devoted to his two young daughters, the elder of whom was born in 1932. His own research had always been his great and absorbing interest, but he was deeply interested too in music, and had played the violin since he was a boy, and music had given him the keenest pleasure all through his life. He enjoyed speaking in public, and was an attractive lecturer, clear, concise, and always interesting.

The work at Fairlie was extremely arduous and exacting and it put a continuous drain upon his vitality. In March of this year he developed an acute gland infection complicated by pneumonia and from this he never recovered.

By his death in April the Navy lost a vigorous and wise Scientific Officer, his Laboratory at Cambridge a brilliant, reliable and kindly colleague, and the world a man of outstanding character who was rapidly establishing himself as a leading authority on molecular adsorption.

ERIC K. RIDEAL.

HENRY JULIUS SALOMON SAND.

1873—1944.

Dr. H. J. S. Sand, who died at Nottingham on October 18th, 1944, after a short illness, was born in Dundee on December 7th, 1873. He attended the High School of that City, continued his scientific studies at the Realgymnasium in Dresden, and, after a short period at the Dresden Polytechnic, where Hempel was one of his teachers in Chemistry, proceeded to Zurich and there carried out research under Bamberger at the eidgenöss Polytechnicum, where he was awarded the degree of Ph.D. Part of this work was published conjointly with Bamberger and Büsdorf under the title " Uber die Einwirkung concentrierter Schwefelsäure auf Nitrosoalphyle " (*Ber.*, 1898, **31**, 1513), this being Sand's first scientific publication. In the same year he became a Fellow of the Chemical Society.

He then worked for a short period with Ramsay at University College, London, and from 1899 to 1901 he was a Bowen Research Scholar at Mason College—now the University—Birmingham, working under Professor Percy Frankland, during which time he began the long series of researches in electrochemistry upon which his high reputation as a chemist is largely based.

From 1901—1914, Sand was Lecturer and Demonstrator at University College, Nottingham, on the staff of Professor Kipping, and in 1905 received the degree of D.Sc. from the University of Birmingham.

In 1914 he became Senior Lecturer in Chemistry at the Sir John Cass Technical Institute and from 1921 until 1938, when he retired, he was Head of the Department of Inorganic and Physical Chemistry, becoming a Fellow of the Institute of Chemistry in 1920.

Sand published his scientific investigations in forty-six papers between 1898 and 1944 and in addition published his " Electrochemistry and Electrochemical Analysis " in three volumes between 1939 and 1941, this work summarising the state of knowledge of the subject from both the theoretical and the practical aspect.

Although Sand will chiefly be remembered for his publications concerning electrochemistry and electrochemical analysis, he also published a number of papers on other scientific subjects, including thermodynamics, diffusion, hydration of ions, strong electrolytes, metal hydrides, and the interaction of potassium tetroxide with ice and with dilute sulphuric acid.

His work on electrolytic analysis revolutionised this subject and provided methods which were accurate and rapid, thus contributing to the growing popularity and importance of these methods of analysis not only in academic work but also in industrial control processes and research. Sand devised many useful and ingenious pieces of apparatus, some of which are notable in that they can be constructed mainly from materials found in all laboratories, thus illustrating that important research can still be carried out without the use of expensive and elaborate apparatus. In this connection his papers " New Apparatus for Electrolytic Analysis " (*Analyst*, 1929, **54**, 275) and " The Separation of Metals by Internal Electrolysis " (*ibid.*, 1930, **55**, 309) are of particular interest.

During the latter part of his long period at the Sir John Cass Institute, Sand gathered around him a band of research students who carried out a number of investigations on electrometric methods of analysis, and many of these, as well as many of his former students and colleagues, will feel his loss very deeply, not only because of his scientific ability but also because of his great personal qualities. He was always very ready to help the young student and indeed anyone who required his assistance and advice. Those who knew him will remember his quiet humour and his modest and kindly personality. He was interested not only in scientific matters but in all public issues, although he took no prominent part in public life.

He is survived by his widow and only son, who is now serving with the Army in Africa, to whom all his friends will desire to extend their sympathy.

James G. Fife.

JAMES NETHERWOOD SUGDEN.

1894—1944.

James Netherwood Sugden, born on March 27th, 1894, at Silsden, near Keighley, Yorkshire, was killed in London by a flying bomb on July 11th, 1944.

Left an orphan at an early age, he was brought up by a grandmother, who, being confined to the house in her latter years, relied on him to represent her at the principal ceremonial events in the neighbourhood, particularly at funerals of her contemporaries. To these early experiences may be attributed perhaps his somewhat grim sense of humour and his ability to face the gloomier transactions of life with apparent equanimity.

In 1905 he entered the Trade and Grammar School, Keighley, where his interest in chemistry was aroused by the teaching of an old student of the Royal College of Science, Harry Harper. From 1911 to 1913 he was a student at the Technical College, Huddersfield, whence he proceeded to the Royal College of Science as the first of a long line of Keighley Grammar School boys subsequently drawn to the laboratories at South Kensington. In 1914 he was awarded the Associateship of the Royal College of Science with First Class Honours in Chemistry, the Neil Arnott Studentship of the University of London, and a Royal Scholarship.

His work as a research student was soon diverted to problems related to the war; and in this connection

he became, in effect, the personal scientific assistant to Professor H. Brereton Baker. Later he obtained a General Service Commission in the Army and was concerned with a variety of chemical investigations bearing on new developments in warfare. When the enemy introduced the use of " gas," he took part in some of the early trials with this new weapon. He was among those who, in the course of an experimental gas attack on Salisbury Plain, had collected air samples at various points by breaking the seals of a number of evacuated bulbs and were then ordered by a notably senior officer to take samples in a second trial by " opening the other ends " of the same bulbs; but he, probably more than anyone, appreciated the humorous side of this attempt by superior military authority to override the laws of nature. To him fell also certain unpopular tasks, such as the disposal of leaking cylinders of some of the more lethal experimental war gases; duties that he performed with characteristic aplomb.

His main contribution to the war effort, however, was in connexion with water supplies. Under the direction of Professor Baker and Colonel Horrocks of the Army Medical Service, he was largely responsible for the technical development of methods and equipment for countering possible enemy action in poisoning or infecting sources of drinking water and for purifying by chlorination water from rivers or canals that was otherwise unsafe for consumption by the troops. A number of plants designed for these purposes were mounted on lorries or on barges and despatched to France. The question of water supplies for the Mesopotamian Expeditionary Force called for special consideration in view of the high risks of waterborne disease in a country where the rivers were also the time-honoured depositories of garbage and sewage and where the temperature during a large part of the year was particularly favourable to the multiplication of micro-organisms. The problem was attacked energetically, and plants of considerable size were constructed for treating river water by sedimentation, alum injection, filtration (through moving sand filters), chlorination and dechlorination. Some were designed as stationary plants to be set up at suitable places on the banks of the rivers Tigris and Euphrates; others, mounted on barges, as mobile plants, to be towed up these great waterways as the army advanced. In the scientific development of this equipment and in the training of the necessary technical personnel, Sugden—then a subaltern (subsequently Captain) in the Inland Water Transport section of the Royal Engineers, attached to the War Office—played a leading part. He had the satisfaction of seeing over a dozen complete plants, valued at several hundred thousand pounds, shipped to Iraq in 1917; and of going out to that country in 1918, when he found most of them in efficient operation.

In October, 1919, Sugden joined the teaching staff of the Royal College of Science (Imperial College of Science and Technology), where he remained for the rest of his life. He was promoted to Lecturer in 1922, and to Senior Lecturer in 1943. He was an excellent teacher. His lectures were models of clarity: he took much trouble in selecting his material and arranging it in a logical sequence, and had a happy knack of " putting it over " in a way which made it acceptable even to lesser intelligences. In the laboratory he caught and held the interest of students, and if his replies to their more ill-considered questions were apt to be disconcerting, they soon realised that his purpose was the worthy one of inducing them to do some thinking for themselves. Those who judged from his stooping figure and his features (so inspiring to the cartoonist) that they had found someone out of whom a rise might be taken, soon realised their mistake: the overt expression of his wrath could subdue; the exercise of his mordant wit could annihilate. From his desk in a corner of the " First Year " Laboratory he gazed dispassionately for a quarter of a century at successive generations of students, discounting routine enquiries by the display of a number of printed notices, but always ready to give personal advice when the situation warranted it. Students recognised him as a " character "—and bestowed their affection accordingly.

Never a robust man, his activities as a research worker were restricted by the need to harbour his energies. His most important investigation was on the hydration of salts in aqueous solution by a partition coefficient method. From a careful examination of a number of salts of the alkali and alkaline earth metals it appeared that for a given salt at a specified temperature the " hydration number " was practically constant up to " normal " concentration. Moreover, for a series of salts of two different metals (or of two different acids) there was a constant difference between the hydration numbers of corresponding salts; indicating that the hydration of a dissolved salt, like its equivalent conductance at infinite dilution, could be regarded as made up of two separate contributions, one characteristic of the cation, and the other of the anion. This additive relation was found to hold even for salts for which the apparent hydration numbers were negative (potassium nitrate and chlorate). In order to explain such negative values of hydration Sugden postulated that only cations are actually hydrated and that anions make negative contributions to the hydration number through a depolymerising effect on water. He showed also that there was a relation between the viscosities of salt solutions and the hydration numbers.

The results of this investigation (J., 1926, 174) were remarkably consistent and represent a contribution to our knowledge of aqueous electrolyte solutions the importance of which may not yet have been fully recognised. He was awarded the degree of Ph.D. in 1924 for a thesis embodying part of this work. He had planned to extend the investigation to the correlation of hydration with other properties of electrolyte solutions, but was obliged to abandon the programme because of eye strain. He made some interesting observations on phase reversals in emulsions, and devised a number of useful lecture experiments. As a practical worker he displayed much ingenuity and took pleasure in securing a maximum of simplicity and neatness in setting up apparatus. It is greatly to be regretted that recurrent periods of ill-health prevented him from continuing research work in his later years.

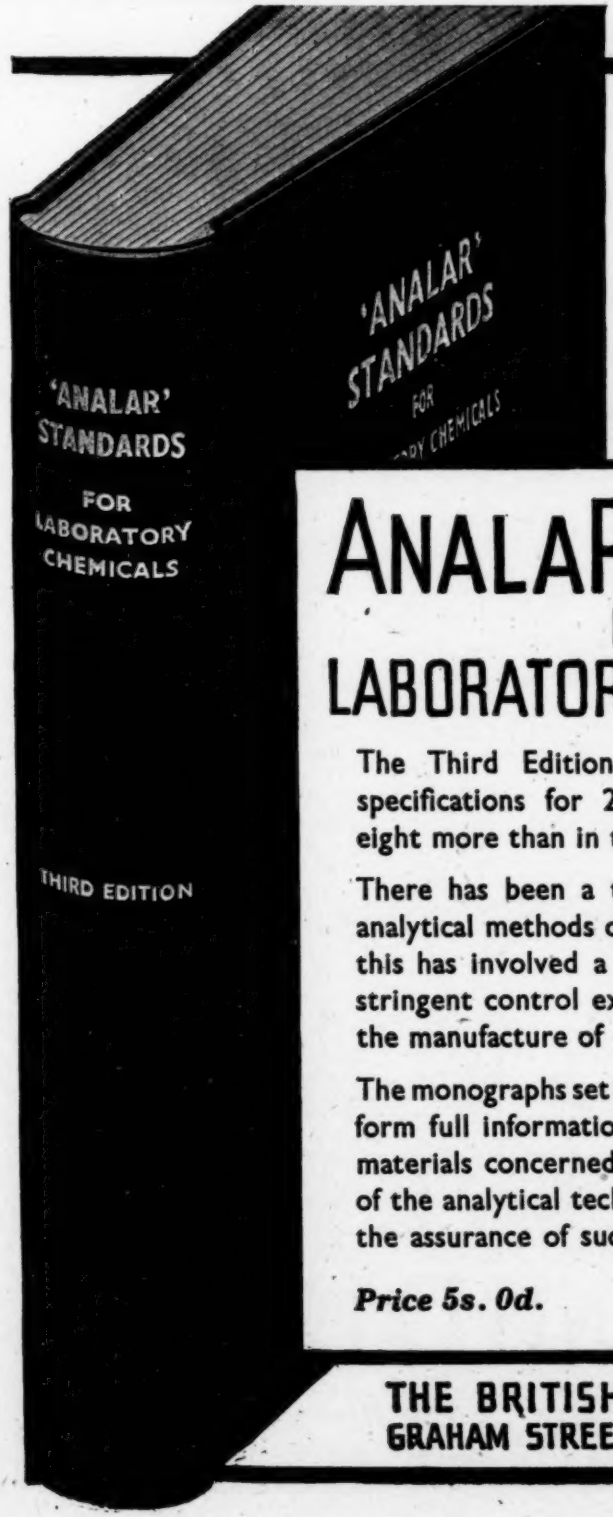
Sugden was an individualist. From his early youth he had been accustomed to fend for himself and to take full responsibility for his own affairs. He expected little from mankind, and was thus spared many possible disappointments. He deliberately limited the circle of his friends and the range of his interests, lest they should become a burden to him. From most organised groups of people he stood apart, and was the despair of those who sought his support for societies and clubs; but among a small group of his chosen friends he was happy, and his shrewd, dry humour would then find expression in conversation that often rose to brilliance. But for the most part he was a lonely man, and one who had learned to bear, if not to enjoy, a solitary life. His reference to a holiday in Touraine as having been spent " sitting under a banana tree reflecting on death, decay, and strong electrolytes," and his claim never to have been to a cinema, were largely figures of speech but nevertheless indicative of a real distaste for being caught up in a crowd.

He spoke French and German with some fluency and derived much quiet amusement from the exercise of his wit in these languages—to the delight of the wise and the discomfiture of the foolish. His individuality was much in evidence in the choice of his minor interests : he could speak with some authority on the seasonal variation in the exchange value of the French franc, on British silver coins issued since the reign of George I (of which he had a fine collection), and on the wines of Burgundy. To these diverse matters, as to his scientific work, he brought a characteristic acuteness of mind and a highly original outlook. In human affairs he showed an almost intuitive understanding of other people's views and feelings that enabled him to predict, often with uncanny accuracy, their actions under given conditions.

From the vast tapestry of life he selected for study a few particular areas. His artistry led him to choose neither the more highly coloured nor the more representational patches, but rather those that seemed somewhat dull and undistinguished. His genius enabled him to show that there was something unexpectedly interesting or bizarre in their structure or arrangement—a queer twist in the threads, an unsuspected knot, a peculiar relation of coloured strands—that threw a new light on the make-up of the whole gaudy pattern.

To him humans were nothing if not individuals. To those of us who held him in esteem and affection he was a very real and unusual person whom we remember as " J. N."

H. J. T. Ellingham.



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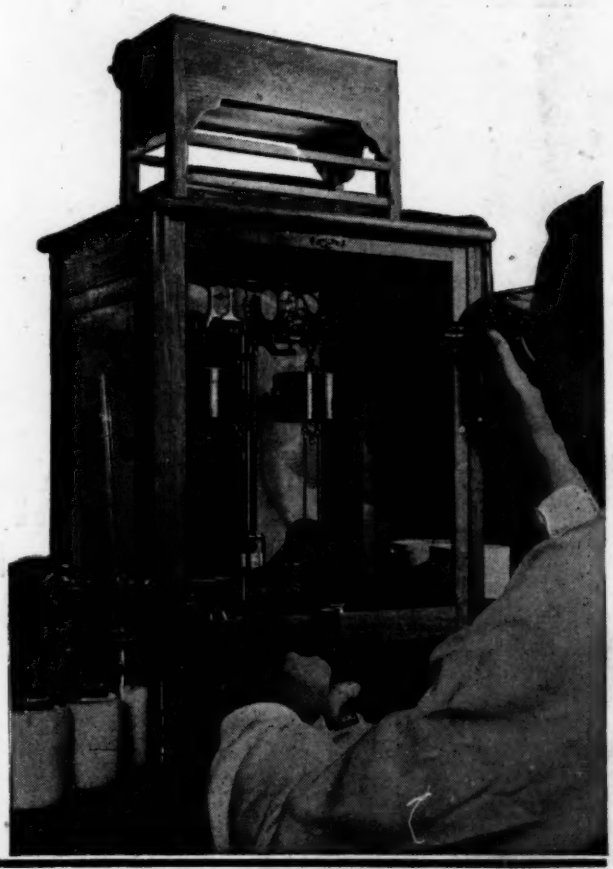

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